Conformable Hybrid Systems for Implantable Bioelectronic Interfaces

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Conformable bioelectronic systems are promising tools that may aid the understanding of diseases, alleviate pathological symptoms such as chronic pain, heart arrhythmia, and dysfunctions, and assist in reversing conditions such as deafness, blindness, and paralysis. Combining reduced invasiveness with advanced electronic functions, hybrid bioelectronic systems have evolved tremendously in the last decade, pushed by progress in materials science, micro- and nanofabrication, system assembly and packaging, and biomedical engineering. Hybrid integration refers here to a technological approach to embed within mechanically compliant carrier substrates electronic components and circuits prepared with traditional electronic materials. This combination leverages mechanical and electronic performance of polymer substrates and device materials, respectively, and offers many opportunities for man-made systems to communicate with the body with unmet precision. However, trade-offs between materials selection, manufacturing processes, resolution, electrical function, mechanical integrity, biointegration, and reliability should be considered. Herein, prominent trends in manufacturing conformable hybrid systems are analyzed and key design, function, and validation principles are outlined together with the remaining challenges to produce reliable conformable, hybrid bioelectronic systems.

1. Introduction

Thin-film and thinned electronics expand the integration of electronic circuits to non-semiconductor carrier substrates with large surface area and mechanical compliance. Applications range from displays, photovoltaic panels, consumer electronics, and Internet of Things (IoT) to wellness and medical technologies. In the past decade, significant efforts have been deployed to exploit these technologies to design and manufacture conformable bioelectronic interfaces.

Mechanical compliance is a critical specification for the long-term integration of on-skin devices and implants with a biological host. The latter is largely composed of soft tissues, with Young’s moduli \( E \) in the range from 100 Pa to 10 MPa (excluding bones and cartilage), and sustains different physiological dynamic behaviors, e.g., repeated displacements of hundreds of micrometers at 1 Hz in the heart or brain, volumetric changes up to 8% in the heart, or large flexion and angular displacement in the skin or spinal cord. In contrast, electronic materials are stiff, with the elastic modulus in the range of 1 GPa (organic materials) to 100 GPa (inorganic materials) and rigid, bearing little strain without displaying mechanical failure or defect generation. Interfaces between such disparate biological and man-made materials suffer therefore from a mechanical mismatch that hinders reliable and continued device function in the body.

Several approaches have been used to engineer mechanical compliance within an electronic device or circuit. Outcomes of such conformable circuits include improved mitigation of foreign body reaction (FBR) in vivo compared to rigid interfaces, access to so far unreachable regions, and bidirectional communication with high spatiotemporal resolution with the biological host.

Monolithic integration of electronic devices and circuits on semiconductor wafers offers extreme miniaturization and very high device density (e.g., \( >10^8 \) transistors \( \text{mm}^{-2} \)), Intel FinFET Technology nodes. Such large scale of integration cannot be achieved for electronics prepared on conformable carrier substrates, as this class of devices employs lower performance device materials and polymeric substrates with low chemical and/or thermal stability leading to limited lithographic resolution and large transistor sizes. These constraints typically worsen as the compliance of the substrate increases. Some of the highest device densities reported to date are \( >10^6 \, \text{cm}^{-2} \) on flexible substrate and \( 347 \, \text{cm}^{-2} \) on stretchable carrier.

Conformable hybrid systems leverage the performance of standard complementary metal-oxide-semiconductor integrated circuits (ICs) and the compliance of discrete flexible or stretchable components and carriers, to effectively provide high-performance and mechanically compliant electronic circuits. They call for new
developments in materials, microfabrication processes, systems’ integration, and biomedical engineering to deliver reliable, long-term, safe and precise communication inside the body. Target biological tissues are many, with prime applications within the central nervous system,[7,12] the peripheral nervous system,[13] the cardiovascular system,[14,15] but also other organs.[16–18] Conformability is a paramount property for these bioelectronic interfaces, ensuring both intimate contact for high efficacy and minimal invasiveness for biointegration.

In this Progress Report, we review recent research efforts in the design and manufacturing of conformable hybrid systems, and report on their applications as bioelectronic interfaces. We describe the systems’ functional complexity, performance, and maturity, and identify global design trends and current trade-offs. We use two prominent examples, i.e., microelectrode arrays[12,19,20] and light-emitting diode arrays,[21,22] to illustrate key concepts and challenges. We conclude by proposing a technological roadmap for the next-generation conformable, hybrid bioelectronic systems.

2. Conformable Bioelectronic Systems

Bioelectronic systems are physical interfaces between a living biological entity and a man-made, electronic circuit that records, transmits, and/or elicits physiological information. A bioelectronic system has three main functional blocks (Figure 1). The “transducers” block (block 1) establishes dialog functions between the biological tissue and electrical/electronic devices that range from simple electrodes to transistor circuits, via organic electrochemical transistors, optoelectronic devices, microfluidic and ion pumps, and a variety of sensors. Flexible “interconnects or leads” (block 2) link the transducers to the electronic circuitry (block 3) that provides switching, signal amplification, filtering, and processing capabilities, as well as powering and telemetry modules. Current implantable medical devices such as a cardiac pacemaker or a deep brain stimulator follow this general scheme.[23–25] The active electronics (block 3) are embedded in a hermetic casing (titanium- or ceramic-based)[26,27] with low channel count (from 4[28] to 21[29]) electrical feedthroughs. Multipolar leads (block 2) next connect to discrete electrodes (block 1) positioned at the location targeted by the therapy.

Current research efforts in “conformable” bioelectronic systems focus on engineering materials and subsystems within and beyond this modular architecture, and improving the biointegration of man-made systems. The aim is to design miniaturized electronic systems that naturally interface and/or envelop the convoluted surfaces of organs, and efficiently and autonomously interact with them. Approaches combine innovative soft materials that display built-in mechanical compliance, transducing capability, and processability with designs that integrate hard electrical/electronic materials into compliant form factors.

2.1. Block 1: Microfabricated Transducers

Transducers convert variations of a physical signal into electrical information and vice versa. Sensing components to detect such signals are usually prepared in thin-film format and include electrodes that record biopotentials, active transistors such as ion-gated field-effect transistors (IFET)[30] or organic electrochemical transistors (OECT)[31] that measure biosignals or the concentration of specific chemical species, physical sensors, e.g., strain gauges,[32] temperature sensors,[33] pH sensors,[15] or integrated photodetectors.[34] Conversely, the bioelectronic interface can deliver information to a selected biological system in the form of electrical pulses via stimulation electrodes[7] or transistors,[35] pulsed light...
Advances in microtechnology allow for the integration of several of these modalities within one bioelectronic system.

2.2. Block 2: Interconnects

Interconnects, alternatively named leads or cables depending on their physical embodiment, are either the implantable or the transdermal link between the transducers and the electronic hardware. They are the electrical skeleton of the bioelectronic system; they transmit electrical signals to and from the transducers (block 1) and instrumentation hardware (block 3).

In the modular design, currently used in medical devices, interconnects are long, hermetic leads with a finite number of connections, bundled into a minimum volume to prevent the risk of infections propagating along them. The cable is flexible to accommodate surgical positioning and repeated mechanical loading. Except for auditory implants and research implants, the cable is detachable from the electronic hardware via a connector. Today, there is no consensus nor a technological solution to provide robust, reliable, compliant, and high-throughput...
cable–connector systems, but rather a plethora of design-specific options.\cite{39}

In an integrated miniaturized format, interconnects are patterned directly on the carrier substrate and over a large surface area (>cm²). They combine low sheet resistance (ideally, <10 Ω sq.⁻¹) with precise patternability and high degree of mechanical deformability. Metallic films are the preferred choice of materials to form interconnects. Their layout as well as integration in the material stack must be engineered so that mechanical strain, applied by bending, stretching, in one or multiple axis, can minimally impact the electrical performance. Common strategies include positioning of the metallic film in the mechanical neutral plane of the structure,\cite{40} strain relief patterns such as serpentine layout,\cite{41} and engineering built-in elasticity.\cite{42–46}

### 2.3. Block 3: Embedded Electronics and Telemetry Module

On-board electronics are occasionally embedded as bare and thinned dies in the compliant substrate\cite{47} but are usually implemented in the form of printed circuit board (PCB) modules encapsulated in hermetic packages, and connected to a telemetry unit for wireless communication with external transceivers. The PCBs host high-performance mixed-signal and digital very-large-scale integration circuits to filter, amplify, and process biological signals, and/or deliver streams of electrical pulses to elicit a biological response.\cite{48} Wireless data and power transmission schemes can be based on electromagnetic (EM) coupling,\cite{49,50} induction coupling, and infrared (IR)\cite{51} or ultrasound (US) transmission,\cite{52} and integrated either as rigid elements\cite{13,51} or thin films.\cite{49,52} Hybrid systems combining thin film–based electronics with rigid thinned chips on a compliant carrier promise further miniaturized systems.

A major challenge remains in the design and integration of efficient powering units. Although research is on-going for flexible batteries,\cite{53} their electrical and mechanical performance currently does not match the needs for power-hungry wearable and implantable bioelectronic systems. Battery-less designs, such as capacitively coupled interfaces,\cite{52} are exciting alternative but remain limited to low channel counts and modest data transfer.

### 3. Function and Compliance of Bioelectronic Systems

The complexity of a conformable bioelectronic system is defined in terms of number of components, manufacturing technology, function, mechanical compliance, and level of integration. Figures 2 and 3 display representative maps of current implantable bioelectronic systems, plotted against the number of channels (components), functions and mechanical compliance. The level of integration increases with high channel counts, multiple modalities, and multiaxial compliance, hybrid integration being the ultimate solution combining function efficacy and flexibility today.

### 3.1. Function and Integration

We have identified five main categories of bioelectronic interfaces (Figure 2): flexible and stretchable microelectrode arrays, multimodal transducers, dust-like systems, discrete transistors and arrays of transistors, and rigid integrated systems. A large portion of the reported compliant bioelectronic devices offers simple function and integration (Figure 2). For example, passive electrode arrays are a popular interface to communicate with electrogenic cells and tissues. A wide range of biological phenomena can be observed with one or a matrix of extracellular electrodes.\cite{7,20,54–58} In addition, the same electrode may be used to deliver electrical stimulation to a local area of the tissue.\cite{7,59} To achieve higher resolution activity mapping, the number and density of electrodes are increased so that simultaneous recordings from a population of cells are collected with high temporal responses.\cite{55,58} This type of technology finds important applications in brain recordings. Passive arrays have been demonstrated both with flexible and stretchable carrier substrates.\cite{7,20}

The next level of complexity describes systems that include active, multimaterial electronic components integrated on compliant substrates. The simplest examples include thinned silicon transistors integrated on plastic foil,\cite{60} inorganic and organic thin-film transistors (TFTs)\cite{30,31,35,61–63} and light-emitting diodes (LEDs).\cite{64,65} Recording of physiological activity via a transistor rather than a passive metallic electrode provides local signal amplification and opportunity for active addressing and multiplexing.\cite{53} In recent years, TFTs have been integrated onto conformable substrates for on-organ high spatiotemporal mapping with >64 recording channels.\cite{12,19,33,66–71}

Few “complete” bioelectronic systems, where distinct functions are integrated together within a miniaturized, compliant and standalone system, exist. A notable example is the retinal implant system Argus II (Figure 2).\cite{72–74} Such a level of integration poses significant challenges as it requires combining powering, data transmission, and processing functions, i.e., advanced electronic circuits, with soft transducing arrays, all the while ensuring mechanical integrity, robustness, and hermeticity.\cite{75}

### 3.2. Biomechanics and Biointegration

Soft biological tissues are characterized by complex mechanical behavior: they usually display nonlinear, anisotropic, and viscoelastic responses, and sustain dynamic loading paced by breathing, cardiac cycles, and macroscopic body movements.

The mechanical mismatch between biological matter and materials commonly employed in bioelectronic systems may be quantified by comparing static parameters, i.e., Young’s modulus E, and dynamic responses, i.e., reversible mechanical loading cycles. The static mismatch spans several orders of magnitude with moduli of about 200 Pa in brain tissue, 2 MPa in dura mater, and 1–5 GPa for polyimide, SU-8, and Parylene-C, 170 GPa of silicon, 250 GPa for platinum (the most used metal for stimulation in clinical devices), and 300 GPa for SiC film (a promising material for thin hermetic encapsulation).\cite{1,76,77}
The insertion of the bioelectronic system in vivo triggers an FBR that the mechanical mismatch between the tissue and the device usually exacerbates. Minimizing this mismatch and associated FBR is a design strategy that is being explored by several research groups. The two most widely adopted approaches are the use of soft, tissue-like, carrier materials and/or the miniaturization of the device/system footprint, especially the dimension parallel to the main radius of curvature of the system.\textsuperscript{[7,59,78]} Ultraminiaturized systems such as dust or moth-like devices\textsuperscript{[13,79–81]} offer rigid alternatives to engineering mechanical compliance for minimally invasive systems. Flexible substrates, i.e., plastic foil,\textsuperscript{[55,58,68]} and anisotropic form factors such as thermally drawn fibers\textsuperscript{[82–85]} enable high bendability, down to sub-millimeter bending radius for <10 µm thick foils.\textsuperscript{[86–88]} To conform nondevelopable surfaces such as the cortex or deploy 3D structures, elasticity may be engineered within the stiff polymers to form 2D meshes.\textsuperscript{[43,89,90]} Alternatively, the bioelectronic system may be manufactured and/or integrated within elastomeric materials to conform complex 3D geometries and accommodate significant multiaxial deformation (strain > 5%).\textsuperscript{[7,20,91–93]}

A natural trade-off between conformability and function of implantable technologies is illustrated in Figure 2 and reflects the practical implications of the given design. Today, complex electronic functions, which can only be integrated from inorganic semiconducting materials, cannot be combined with biomimetic compliance. The selection of suited technologies and associated materials stems therefore from careful engineering choices, with some applications prioritizing advanced electrical functionality over mechanics and vice versa. While IC miniaturization and development are progressing to provide enhanced circuitry in reduced footprints, an interesting and recent development toward implementing electrical function in mechanically compliant systems is the integration of
gel-based materials in bioelectronics. Hydrogels, which contain up to >90% water, display tissue-like softness. While the manufacturing and patterning steps of these soft materials are still at an early stage,[91] one can anticipate ultrasoft materials will unfold opportunities within a further class of conformable bioelectronic technology.

4. Two Case Studies: Conformable Recording Electrode Arrays and Flexible Light-Emitting Diode Arrays

In the following section, we assess the two most common classes of bioelectronic systems (recording electrode arrays and light-emitted diode implants) and benchmark their performance against conformability.

4.1. Recording Electrode Arrays

Arrays of electrodes placed on the surface of the brain enable measurements of local field potentials (LFPs) that visualize the collective firing of groups of neurons. In the clinical scenario of drug-resistant epilepsy, this type of signals is used to localize the brain region from where epileptic seizures originate.[94] Similarly, measuring the polarizing potential at the surface of the heart can unveil the location of lesions in the myocardium that induce imbalance in the heart rhythm. Increasing the spatial sampling by scaling up the number of electrodes available on bioelectronic interfaces may give access to localized information that is impossible to monitor with current clinical electrodes.[95] Therefore, increasing the quality of the signal recorded with small electrodes,[31] the number and density of recording sites[12,96] are advances of great interest. In addition, the manufacturing of the arrays on soft and compliant carrier substrate further improves their integration with soft and dynamic systems such as the surfaces of the brain or the heart. Notable examples of recording arrays reported in the literature are presented Figure 3, ranked by their number of channels and overall mechanical compliance.

Several examples of brain recording arrays with hundreds of channels have been reported, both in passive and active configurations. A thin poly(dimethylsiloxane) substrate with gold-coated TiO2-nanowire-based interconnects enables fine-scale recordings of potentials at the surface of the brain up to 32 channels.[20] The combination of low-modulus substrate material and low-thickness design enables the array to comply to the curved surface of the brain and acquire stable recordings of LFPs over 3 months.

Figure 3. Conformability of passive and active implantable devices for biopotential recording. The x-axis represents the conformability of the device and the y-axis represents the number of recording channels present on the device. Each symbol represents a device published in a peer-reviewed publication. The colour of the symbol identifies in which cluster from Figure 2 the device belongs to. A circle (•) represents a passive recording device and a triangle (▲) represents an active recording device. A) Capacitively-coupled transistor array for the multiplexed high-resolution recording of heart surface activity. Reproduced with permission.[92] Copyright 2017, Springer Nature. B) PEDOT:PSS microelectrode array recording on the surface of the human brain with large clinical-like electrodes for comparison of signals. Adapted with permission.[122] Copyright 2018, Wiley-VCH. C) Stretchable microelectrode array on thin elastomeric membrane for conformable contact to the brain. Reproduced with permission.[92] Copyright 2018, Wiley-VCH. D) TFT array based on organic materials for the multiplexed recording on the brain surface. Reproduced with permission.[92] Copyright 2016, Wiley-VCH. E) Ultrasonic dust recording on the surface of a peripheral nerve. Reproduced with permission.[122] Copyright 2016, Cell Press. References in alphabetical order: Blaschke 2017,[30] Chao 2010,[132] Chung 2014,[13] Escabi 2014,[44] Fang 2017,[66] Ganji 2018,[75] Gkogkidis 2017,[74] Khodagholy 2015,[94] Khodagholy 2016,[94] Kim 2010,[94] Kim 2012,[12] Lee 2016,[69] Lee 2017,[70] Liu 2015,[90] Marcoleta 2018,[122] Minev 2015,[7] Muller 2015,[49] Park 2014,[97] Rubehn 2009,[93] Seo 2016,[13] Tybrandt 2018,[20] Viventi 2010,[67] Viventi 2011,[12] Xie 2015.[95]
Increasing the number of electrodes calls for active addressing. In the case of an $M \times N$ grid of electrodes, a passive array needs all connections ($M \times N$) to be physically wired, whereas a matrix-addressable array only requires $M + N$ switched connections. Reducing the number of outward connections, especially when conducting long-term in vivo evaluation, is highly desirable as it can both simplify the electrical wiring scheme around the experimental hardware and drastically reduce the mechanical and biological burden on the interface between the body and the external equipment.

We anticipate the next-generation electrode arrays will host on-board amplification and digitization capabilities integrated directly on the conformable carrier substrate to significantly reduce the footprint of electrical connections leaving the body. Ultimately, conventional electronic components, i.e., bare dies will be integrated directly on the soft carrier substrate. Hybrid systems hosting thin-film devices close to the soft tissue and rigid high-performance electronics further away will bring the synergy required to develop the next-generation complex devices. Some initial designs are presented in refs. [49,97]; further development will certainly follow in the near future.

4.2. Light-Emitting Diode Implants

The rise of optogenetic control of neurons has brought the need for integrated light sources on bioelectronic probes, in addition to applications such as wearable LED-based devices for phototherapy applications. Through genetic engineering or viral transfection, specific neurons can express a light-sensitive protein, an opsin, ion channels that are triggered upon light stimulation of a given wavelength. By controlling the type and location of the opsin-expressing neurons, specific neuroengineering or neuroscience experiments can be conducted where a specific neuron population can be selectively stimulated. A simple method to deliver light to a biological tissue employs stiff optical fibers coupled to an external light source. However, such an approach often restricts in vivo experiments to single wavelength, single point stimulation, and tethered monitoring. Miniaturized and addressable light-emitting diode arrays offer an interesting alternative for spatially addressable in vivo optogenetics. Several designs are being explored and are summarized in Figure 4.

The recurrent trade-off between performance and conformability is clearly visible in conformable light-emitting arrays. Light delivery is achieved either by integrating commercially available, packaged, or bare die LEDs with small footprint or through transfer printing of ultrathin microLEDs based on GaAs or GaN materials onto the compliant substrate. Transferred thin GaN or AlInGaP microLEDs have thicknesses in the order of a few micrometers, compared to commercially available microLEDs of several tens of micrometers of thickness. The transfer and integration of such small components onto miniaturized and polymer-based probes pose significant challenges including precise alignment (sub-millimetric) and reliable electrical interfacing to interconnects. An encapsulation step is also required to protect the semiconductor devices from water ingress in vivo using water barrier materials such as Parylene-C, epoxy resins, or polyisobutylene (PIB). Multimodal systems can host microLEDs of distinct emission wavelengths combined with drug delivery or optical sensing elements. Such systems are developed to investigate complex biological mechanisms such as pain and other neural circuits.

Most examples reported in the literature integrate one or a few individual LEDs (Figure 4). A common strategy to engineer flexibility and even stretchability in microLEDs arrays is the use of buckled, plastic-based interconnects to power and address the optoelectronic devices on an elastomeric substrate. Besides the microfabrication and packaging challenges, a strategy is needed to ensure uniform current injection, reduced series resistance, and improved heat extraction in the LEDs. Both electrical and optical energy losses occur within the LEDs and the surrounding tissue during the electro-optical conversion process, with most of the loss due to Joule effect. A remarkable example of bendable, high-density, microLED is the optoelectronic cochlear implant by Klein et al. over a hundred GaN microLEDs were integrated onto a transparent epoxy resin with improved thermomechanical behavior compared to their integration on standard polyimide substrate. Temperature rise was limited to $1 \, ^{\circ}C$—a safe biological increase—when operating the microLEDs at 10 mA, 10 kHz, and a 10% duty cycle thus providing an optical (emitted) power density of 497 mW mm$^{-2}$, sufficient for optogenetic experiments. Control and addressing of each LED are however not yet achieved.

Careful system-level design is required when integrating large numbers of light sources for light stimulation with high spatial resolution. Using organic thin films or inorganic nanocrystal-based light emitters processed directly on the compliant substrate. Temperature rise was limited to 1 $^\circ$C—a safe biological increase—when operating the microLEDs at 10 mA, 10 kHz, and a 10% duty cycle thus providing an optical (emitted) power density of 497 mW mm$^{-2}$, sufficient for optogenetic experiments. Control and addressing of each LED are however not yet achieved.

5. Maturity of Hybrid Technologies

Assessing the maturity of hybrid technologies involves determining its readiness for operations across a range of environments and uses before it ultimately transitions to commercial and/or clinical products. The interdisciplinary nature of a hybrid technology for conformable bioelectronic systems therefore calls for many validation steps in the domains of materials science, electronics, bioengineering, and the medical sciences.

Manufacturing processes implemented for bioelectronic systems are borrowed from traditional microelectronics, thin-film electronics and microelectromechanical system technologies, and applied to mechanically compliant carrier substrates. These technologies are well established, although optimization and tailoring to polymer-based substrates are still on-going. The maturity of the conformable bioelectronic systems rather depends on often overlooked components, i.e., connectors, encapsulation, and wireless capabilities.
This is particularly challenging when translating the new systems toward medical use where standards and norms govern the approval of a new device.\cite{115,116,117} As new materials and form factors are introduced, existing norms and associated testing protocols become inadequate or obsolete. For instance, in vitro evaluation and validation of the mechanical robustness of a conformable bioelectronic system may require specific electromechanical test benches that are application-dependent and not yet standardized.

Next, preclinical validation in vivo requires the testing of safety, long-term functionality, and efficacy in animal models, each with their associated challenges and different translational value. In medical technology research, rodents are most employed for academic research and proof-of-concept demonstrations, as they are broadly available, financially viable, and approved by ethical and veterinary committees. Larger animal models such as pigs or sheep are typically employed for biocompatibility studies, leveraging the similarity in size and immunodynamics to human biology.\cite{118} Nonhuman primate models are used in translational research, especially for applications in neural interfaces, as monkeys share with the end users (i.e., human patients) many similarities in anatomy and physiology.

![Figure 4](https://creativecommons.org/licenses/by/4.0/)

Conformability of implantable bioelectronic devices with light-emission capabilities. The x-axis represents the conformability of the device and the y-axis represents the number or types of light-emission channels integrated in the system. Each dot represents a device published in a peer-reviewed publication. The colour of the dot indicates the cluster the system belongs to (from Figure 2). A) Silicon shanks with embedded GaN microLED with recording electrodes. Reproduced with permission.\cite{156} Copyright 2015, Cell Press. B) High-density integration of GaN on custom-built epoxy substrate for an optical cochlear implant. Adapted under the terms of the CC-BY Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).\cite{22} Copyright 2018, The Authors, published by Frontiers Media. C) MicroLED integrated on flexible probe with embedded drug-delivery channel. Reproduced with permission.\cite{106} Copyright 2015, Cell Press. D) Miniaturized system for wireless implanted multi-color optical probe in the brain. Reproduced with permission.\cite{118} Copyright 2019, The Authors, published by AAAS. Reprinted/adapted from ref. [18]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/. E) Ultra-miniaturised LEDs powered wirelessly for implanted light therapy. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).\cite{100} Copyright 2019, The Authors, published by Springer Nature. F) MicroLED integrated on a flexible probe with a receiving coil for wireless powering. Reproduced with permission.\cite{105} Copyright 2017, Cell Press. G) A soft microLED platform with integrated strain gauge for the closed-loop stimulation of the bladder. Reproduced with permission.\cite{52} Copyright 2019, Springer Nature. References in alphabetical order: Canales 2015, Jeong 2015, Kim 2010, Kim 2013, Kim 2019, Klein 2018, Komatsu 2017, Kwon 2013, Lu 2014, Lu 2017, Lu 2018, Mickle 2019, Montgomery 2015, Noh 2018, Park 2015, Park 2016, Samineni 2017a, Samineni 2017b, Shin 2017, Wu 2015, Zhang 2019.
cognitive functions.\textsuperscript{[119,120]} Finally, clinical validation is required to demonstrate safety of the device when in contact with the patient and its efficacy.\textsuperscript{[121]} All these validation steps are required to reach clinical evaluation then use, and also depend on the rules set by regional regulation authorities. A good overview of this process is given in ref. \textsuperscript{[24].}

The validation timescale and longevity of a bioelectronic system vary from acute use to life-time treatment. For example, microelectrode arrays for neural monitoring may be required in an intraoperative setting, e.g., for the identification of eloquent brain regions during tumor resection procedures, and used in vivo for <20 min.\textsuperscript{[122]} Conversely, brain–machine interfaces (BMIs) such as motor\textsuperscript{[123]} or speech\textsuperscript{[124]} rehabilitation interfaces are to be used for long periods of time, months to years.

Despite clear medical needs, evaluation and use over extended implantation periods of conformable bioelectronic interfaces are not systematically conducted. One of the main challenges is the reliability and predictability of the device performance over time. The survival of a device implanted in the body requires numerous challenging engineering features; the materials employed must be noncytotoxic and inert to the body’s biochemical environment, the mechanics of the system must ensure an adequate degree of conformability to the tissue, and the outer layers must be resilient against water and ion ingress. This last aspect is particularly important for active electronics, as water and ions have been shown to dissolve or short-circuit elements such as the conductors, the semiconducting layers or the dielectrics in thin film-based devices.\textsuperscript{[125,126]} For passive devices, water and ions’ ingress will lead with time to electrical short-circuits between the individual channels (i.e., finite resistances between individual electrodes through the insulation layer). Traces running in parallel will be subject to crosstalk and the quality of the recorded signals will drop.\textsuperscript{[127]}

Figure \textsuperscript{5} displays a map of implantation time of the categories of bioelectronic systems reviewed in Figure \textsuperscript{2}. Very few bioelectronic systems perform in vivo over prolonged implantation. Conventional implantable electronic systems are encapsulated in rigid titanium modules to perform over years in the body. Conversely, bioelectronic interfaces require innovation in “thin” hermetic packaging; to date, a range of insulating thin film or multilayers are investigated to provide stable encapsulation over weeks to a year of implantation,\textsuperscript{[128–130]} but there is no consensus on the materials choice yet.

Passive flexible and stretchable arrays have been chronically implanted in rodents\textsuperscript{[7,14,20,57,59,91,131]} and large animal models.\textsuperscript{[55,132,133]} Their encapsulation materials include plastics, e.g., polyimide, Parylene-C, and elastomers, eventually combined with thin inorganic dielectric films, e.g., SiO$_2$, SiN$_x$, or SiC.\textsuperscript{[129,130,134,135]} Active implants based on single or multiple microLEDs or thin film transistors systems have been successfully implanted for months using engineered water-barrier materials especially around the LEDs.\textsuperscript{[64,55,103]} No result is reported on long-term encapsulation of the most complex systems (Figure \textsuperscript{2}) as the disparate topography of rigid, thick components combined with flexible and stretchable transducers cannot currently be uniformly encapsulated with thin-film materials.

Another critical design choice for conformable bioelectronic systems is their interface with experimental and/or therapeutic hardware. Feedthroughs, connectors, cables are ubiquitous connectivity solutions in all current prototypes, and wireless systems are still rare.\textsuperscript{[21,52]} There is no recommended approach today for connections and wiring as each hybrid system interfaces with distinct equipment. Careful engineering of robust transdermal ports and connectors is usually required to reliably interface external equipment to the implanted device over weeks or months of implantation. Some studies revealed that the bioelectronic system itself does not fail but its interface to the outside does.\textsuperscript{[116–138]}

In clinical devices such as cardiac pacemakers or deep brain stimulators, the bioelectronic interface is connected with small channel count feedthroughs to a large footprint, stiff hermetic metal, or ceramic can.\textsuperscript{[72–74]} The number of connections fed through the can is limited\textsuperscript{[139]} as they cannot be scaled down in size while guaranteeing sufficient insulation over years. Substantial efforts and innovation are thus needed to bring hybrid integration and high channel count interfaces forward.\textsuperscript{[140]}

6. Challenges for Future Implantable Bioelectronic Interfaces

Conformable bioelectronic systems promise technological solutions to unmet needs in the investigation of biological functions and development of novel medical technology. Recent advances in materials science and engineering outlined in the previous sections are motivating new concepts and designs for wearable and implantable bioelectronic systems. We have also identified several challenges that need addressing before the widespread adoption of these complex systems in biomedical research and their translation to clinical use (Figure \textsuperscript{6}), namely: i) design and processability of soft materials, ii) engineering of thin and compliant hermetic materials, iii) integration of autonomous and compact systems, iv) definition of standard validation protocols suited to new classes of conformable bioelectronic systems, and v) the controlled manufacturing for translation to the clinic.

6.1. Design and Processability of Ultrasoft Materials

Engineering mechanical compliance within bioelectronic systems prompts the development of advanced materials and new fabrication pathways with improved scalability, design flexibility, and robustness. Current approaches leverage the processability of established device materials and polymeric substrates combined with the manipulation of softer materials with enhanced biomechanical match. The latter usually forms the very biointerface that coats the stiffer device materials backbone to the conformable system. An outstanding approach is the introduction of hydrogels to encapsulate the bioelectronic system.

The main idea is to use the soft coating to reduce the apparent stiffness of active thin-film devices developed on flexible foils to lower the inflammation response and therefore promote long-term biointegration (Figure \textsuperscript{6A}). Examples of such gels include aqueous polyrotaxane gel\textsuperscript{[59]} or poly(vinyl alcohol) (PVA) hydrogels.\textsuperscript{[5]} The gels may be dip- or spin-coated or bonded on the microfabricated probe or system. Processing of such gels, especially patterning and controlling of swellability, remains however a challenge.
Another approach explores the manufacturing of the bioelectronic system using entirely soft functional materials such as elastomers and hydrogels (Figure 6B). The function and processing of such devices are currently relatively modest. Yet, devices with an overall Young modulus in the 10 kPa range, which is similar to that of nerve tissue, have recently been demonstrated employing stretchable dimethacrylate-functionalized perfluoropolyether polymer (PFPE-DMA) with embedded tracks of an electrically conductive hydrogel (ECH) containing poly(3,4-ethylenedioxythiophene) (PEDOT)-polystyrene.
Figure 6. Future challenges for next-generation conformable implantable bioelectronic interfaces. A, B) Soft materials and biocompatibility: A) Integration of a soft polyrotaxane gel onto the electrode sites read-out by an organic amplifier array fabricated on a thin flexible Parylene C foil. As visible from histology, the presence of the gel increases the biointegration of the device as tested in vivo. Adapted under the terms of the CC-BY Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).\textsuperscript{[19]} Copyright 2016, The Authors, published by Springer Nature. B) A soft electrode array with an overall 10 kPa Young’s modulus comprising a dimethacrylate-functionalyzed perfluoropolyether polymer (PFPE-DMA) as substrate with embedded tracks of an electrically conductive hydrogel (ECH) containing PEDOT:PSS laid on a soft jelly. The device is comparable to nerve tissue (\(E \approx 10^4\) Pa) unlike standard device materials such as elastomers or flexible foils ("Conventional materials", \(E \approx 10^6–10^9\) Pa). Adapted with permission.\textsuperscript{[91]} Copyright 2019, Springer Nature. C, D) Hermetic encapsulation: C) Thin-film-based strategies for hermetic encapsulation on conformable substrates test structures using materials deposited using chemical vapor deposition (CVD) such as HfO\(_2\) and SiO\(_2\). Different material systems are screened by accelerated ageing at 96 °C in saline solution (PBS). When the water diffuses through the barrier, the control magnesium layers change appearance. Adapted with permission.\textsuperscript{[144]} Copyright 2018, American Chemical Society. D) Amorphous silicon carbide (a-SiC)
sulfonate (PSS). Hydrogel-based electronic devices such as transistors have also been recently reported. Many efforts are currently underway to integrate miniaturized gel-based devices with higher density.

6.2. Hermetic Encapsulation

One of the main limitations for long-term conformable bioelectronic systems is the lack of reliable materials and associated processing of hermetic coating. Sensitive electronic devices as well as parallel metallic interconnects may suffer from corrosion, mechanical failure, and electrical leakage from eventual ingress of water and/or ions through their polymeric carrier.

Water permeability of common plastic foil materials, e.g., polyimide is high enough to allow for the diffusion of ions toward the electronic materials over weeks of exposure to physiological medium. Their water vapor transmission rate (WVTR) is of the order of $10^{-5}$ g m$^{-2}$ day$^{-1}$. For metals and glasses, WVTRs are several orders of magnitude lower, around $10^{-10}$ and $10^{-6}$ g m$^{-2}$ day$^{-1}$, respectively.

Insulating oxides or nitrides are commonly used as barriers in flexible electronic displays; their integration into flexible and conformable systems requires special attention given their native brittleness. Multilayers of these materials can provide long-term water barrier for thin active electronic devices (Figure 6C). However, thin layers of inorganic materials deposited by plasma-enhanced chemical vapor deposition (PECVD) provide good water barrier properties, but often suffer from point defects due to local substrate contamination, topography, etc., which create preferential channels for the ingress of liquids and ions in the underlying interfaces. The chemical vapor deposition (CVD) of Parylene-C, on the other hand, is ultraconformal even to complex topographies. The combination of both types of materials provides superior hermeticity for packaging of bioelectronic interfaces, and high mechanical stability. Such multilayered stack leads to increased effective percolation pathways, thus reduced water permeation compared to a single layer of Parylene-C of similar thickness. Other classes of materials such as silicon carbides offer similar water barrier properties to silicon oxide and can be doped to insulate the electrode area from water (Figure 6D). The quality of the inorganic layer may be improved with deposition processes such as CVD or atomic layer deposition (ALD), thereby further increasing the predicted (hermetic) lifetime of the encapsulated active bio-electronic devices.

Next, the adhesion strength, minimum bending radius, and cyclic fatigue of the thin-film multilayers should be evaluated in accordance to the envisioned application. The adhesion to the carrier material should also be validated. Despite many research efforts, the adhesion of Parylene-C to itself or to metals remains an issue that will need to be addressed in the near future.

6.3. System Integration

The integration of active electronics elements in implantable systems has enabled significant advances both in technology and in the understanding of life sciences. Most examples found in the literature involve experiments that are typically designed to show specific aspects of a device, as opposed to validating a whole system that includes all the necessary components. As bioelectronic systems translate to more long-term applications, complete and autonomous systems should be developed, and avoid, whenever possible, transdermal ports to communicate with external hardware. Today’s medically approved implanted devices are fully integrated and wireless; conformable bioelectronic systems are rarely so. An illustration of one of the most advanced integration is displayed Figure 6E; passive recording electrodes patterned on flexible Parylene-C foil are interfaced with a bare silicon chip (an application-specific integrated circuit, ASIC) that converts the detected analog signals into the digital domain, then relays them by EM coupling to an external receiver.

Another required component is the transmission antenna (Figure 6F); several simple systems have shown the integration of receiving antennas together with multiple light-emission devices. The modulation of the light source may be controlled by choosing the frequency of the input EM wave to the antenna.

Such significant challenges have not yet been fully addressed, and complex, long-term standalone systems have not been demonstrated thus far with flexible transistor arrays’ technology. Concepts for the integration of small ASICs on flexible foils have been reported but either without or acute in vivo validation or not on conformable interfaces. In addition, advances in circuit design are needed to enable mixed-signal embedded systems that can handle analog biosignals, digital driving signals, as well as wireless data and power transfer in a small package.
6.4. Validation

Contrary to conventional medical devices, conformable bioelectronic systems not only need to offer reliable electrical and electrochemical functionality but they should do so upon significant and complex strains. Current validation protocols, defined for rigid implantable systems, are no longer adequate. Novel mechanical testing protocols must be introduced to enable more relevant lifetime predictions and the failure mode analysis of conformable devices. An illustrative case is the mechanical in vitro model that was developed for longitudinal intrafascicular electrodes (LIFE)\textsuperscript{[150]} implanted in the peripheral nerves of the arm or the leg (Figure 6G). To mimic the tension applied to the lead by the limb movement, silicone tubes were stretched in saline solution repeatedly. The lead part of the LIFE was attached to the tubes as in the implanted case. By stretching the tubes, the lead and its anchoring points both undergo mechanical tension that is representative of the implanted configuration, so as to mimic the failure modes observed in clinical cases. As illustrated for the case of the LIFE devices, we anticipate that different targeted tissue will require adapted mechanical models to enable predictive reliability testing.

Another important aspect in device validation is the development of reliable accelerated ageing protocols that can enable lifetime prediction in the body. Most of current state-of-the-art reliability tests are conducted in aqueous solutions such as phosphate-buffered saline (PBS) at high temperature.\textsuperscript{[144]} If degradation mechanisms are governed by diffusion, then Arrhenius’ Law can be used to extract an acceleration factor. This is, however, not representative of all the conditions that induce deterioration in vivo. In an example of subdural brain implants, and more specifically intracortical probes, the foreign body reaction triggered by the man-made device produces significant concentration of reactive oxygen species (such as hydrogen peroxide, $H_2O_2$ with a concentration up to $30 \times 10^{-3} \, m$), creating a highly oxidative environment.\textsuperscript{[151]} Ageing reactors that include this additional chemical input may therefore be able to recreate degradation mechanisms that do not occur (or not as quickly) within a PBS environment. In a significant example, a testing setup has been developed to age intracortical probes with a continuous feed of hydrogen peroxide in the test solution.\textsuperscript{[152]} A closed-loop system is required for the addition of reagent to the solution as it quickly separates into water and oxygen at high temperature (Figure 6H). This oxidation agent has been shown to quickly degrade electrodes compared to standard PBS ageing. In general, we foresee the rise of new test protocols that are tailored to the specific environment of the targeted tissue.

Finally, it is crucial tests are designed based on the complete system, and not parts of it. Interconnects, leads, and other components contribute greatly to the failure of systems in vivo, especially when implanted for long periods of time. For example, a neuromodulation system for the spinal cord may fail when the interconnects between the spinal array and the stimulator moves and leads to a small bending radius. With small movements and over prolonged periods of time, this leads to cracking within the conductor layer and failure of the implanted interface.\textsuperscript{[153]}

In general, standard validation methods used for clinical devices are no longer adequate to assess the robustness of new classes of devices such as conformable bioelectronic interfaces. We anticipate that future protocols will be tailored to specific clinical scenarios, with relevant mechanical, chemical, and thermal inputs that are based on factual observations. Furthermore, the predictive value of accelerated ageing tests will need to be carefully assessed to enable reliable lifetime estimations.

6.5. Controlled Manufacturing and Translation to the Clinic

Beside verification and validation, the translation of new devices for clinical use requires a series of control measures during manufacturing that are intended to guarantee traceability and process control. The use of manufacturing processes derived from the semiconductor industry enables the introduction of in-line tests and statistical methods that are typical of the microelectronics industry. Nevertheless, final assembly steps are usually manual and therefore of challenging control.\textsuperscript{[104]} The introduction of new materials into medical devices requires additional tests such as cytotoxicity and systemic toxicity tests. Toxic materials and chemicals used for processing of the devices (such as solvents and etchants) need to be completely eliminated from the implant and elution tests are needed to verify the absence of residue. Finally, all these steps need to be rigorously documented and archived for future device certification and commercialization.

7. Perspectives and Outlook

As the barrier for entry to the clinic is extremely high, next-generation conformal bioelectronic interfaces will need to convincingly outperform the current clinical devices that they will replace, or else enable impactful new therapies that will significantly improve therapeutic outcomes. On one hand, preliminary demonstrations and proofs-of-concept have shown that seamless integration into the target tissue along with high-density recording and stimulation sites will unfold better understanding of a range of diseases in several medical domains, as well as identify and treat their origin and symptoms.\textsuperscript{[7,12,14]} On the other hand, successful industrial implementations will require innovative solutions to a series of challenging engineering problems that hinder today a full-scale adoption of new bioelectronic systems.

By fully leveraging microelectronic manufacturing capabilities adapted to conformable materials and/or form factors, future devices will benefit from both high density of functional elements thanks to the resolution of lithographic processes, and high mechanical compliance to efficiently interface with the target tissue. The design flexibility introduced by lithographic patterning will also unfold the possibility of rapidly producing devices of different designs that can adapt to different placements and/or subjects. Coupled with current and future high-resolution medical imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT), this will enable personalized bioelectronic interfaces that are
tailor-made for the host body and intended use, akin to current procedures for the design of structural prostheses such as hip implants or vertebral disks. We picture future manufacturing frameworks with medical imaging data integrated directly in the design tools and automated processing lines implemented following the current microelectronics standards.

Tailored bioelectronic interfaces enabled by microtechnology are highly desirable to achieve unmatched specificity when interfacing with precise areas on small peripheral nerves, the spinal cord, the brain, the heart, and internal organs such as around the kidneys, liver or gastric system,[154–156] or the eyes.[17] Such technological evolution must however be accompanied by an adequate shift in the way devices of different designs are validated prior to their commercialization. As each therapeutic application is associated with different technological configurations (e.g., number and placement of recording elements, stimulation thresholds, geometrical constraints due to specific anatomical features, and required mechanical properties), different validation protocols are also required. This will entail a particularly critical change in mechanical testing routines, as future devices will be built with materials that must maintain functionality at high, multiaxial strains. Similarly to what once introduced in the medical device industry for specific tests such as lead flexion test,[153] the validation of future conformable bioelectronic interfaces will therefore require adapted test protocols.

Significant research efforts will be further devoted to integrating together different active electronic functionalities provided by sensing, data processing, and power transfer elements, into a single conformable system. Complex functions will continue to be provided by conventional electronic elements, as research on soft active electronics is still at its outset. Rigid components will therefore still be paired to the soft interfaces, and adequate engineering strategies must be developed to bridge the two worlds, both from an electrical and a mechanical point of view. A challenge that is inherent to hybrid material systems is their hermetic encapsulation. Material interfaces must be engineered so that the embedded thin-film electronics do not suffer from failures due to moisture ingress under physiological conditions in the body over periods of time of the order of years or even decades.

We anticipate advances on all the presented fronts unfolding at a steady pace, with researchers from different fields initially working on separate pieces of the puzzle, and then gradually merging new technological solution in more complex systems. We therefore expect initial demonstrations of simple fully implantable systems such as wireless single-input devices for peripheral nerve stimulation, followed by more comprehensive technological platforms such as large-scale high-density brain recording grids. Upon reaching industrial maturity, it is envisaged that future classes of conformable bioelectronic technologies will revolutionize clinical outcomes by routinely enabling long-sought-after therapeutic approaches that are today at their embryonic stage.

Acknowledgements
The authors acknowledge financial support by the Bertarelli Foundation, the European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement no. 665667, and the Wyss Center for bio- and Neuroengineering (Grant No. W015-2016).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
bioelectronics, electronic functions, hybrid integration, mechanical design, microfabrication

Received: June 19, 2019
Revised: August 20, 2019
Published online: October 14, 2019

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