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Review

Implantable bioelectronics toward long-term stability and sustainability

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SUMMARY

Marrying electronics with biological systems has generated a broad spectrum of potent technologies for biomedical practices, as well as an emerging field of "bioelectronics." Conventional rigid silicon microelectronics-based implantable devices suffer from low biocompatibility and high invasiveness. Also, lack of options for sustainably supplying power and wirelessly transmitting data further limits sustainable operations. During the past decade, remarkable research progress has been made in creating new material concepts and device-engineering strategies toward achieving multi-aspect physical and chemical biocompatibility, sustainable power supplies, and wireless data transmission under implantation. In this Review, we provide an outlook of the development of implantable bioelectronics through the review of these major research directions. Representative concepts and important breakthroughs in material and device innovations are discussed. Challenges and future directions are also posed to usher further research efforts toward realizing bioelectronics with minimal invasiveness, *in vivo* biocompatibility, fully implanted operation, and sustainable power supplies.

INTRODUCTION

Ever since the invention of the first artificial pacemaker in 1932, the development of electronics that go into human bodies to directly interface with biological tissues and organs, so-called implantable bioelectronics, has been rapidly growing to become an important set of tools in medical technologies. To date, implantable bioelectronics have been offering functions in three major categories (Figure 1): (1) symptom alleviation from chronic diseases, as offered by cardiac pacemakers, deep brain stimulators for Parkinson's disease and tremors, and phrenic nerve stimulation for respiratory insufficiency; (2) restoration of lost/degenerated body functions, as offered by retina prosthesis, cochlear implants, and brain-machine interface for neuroprosthesis; and (3) monitoring of tissue status and health conditions, as offered by implantable blood pressure sensors and metabolite sensors.

Despite the remarkable successes and the sizable market for implantable bioelectronics, their developments to date have been almost fully relying on silicon (Si) microelectronics,[1] which possesses several inherent limitations for providing functions with long-term stability and sustainability. With insufficient accuracy when interfacing with targeted pathogenic locations, the implantable devices only have limited treatment resolution, which results in compromised efficacy and non-negligible side effects.[2] Repeated irritations and damage to the tissues from these rigid devices typically lead to prominent inflammation reactions at the implantation sites,[3] eventually causing the rejection of the devices by human bodies. Additionally, the limited lifetime of power sources under body implantation further limits the

Progress and potential

In the applications of implantable bioelectronics, improvements in biocompatibility and operational sustainability have been made from both physical form factors and materials' chemistry, such as making the implantable devices smaller, softer, and less vulnerable to the foreign-body response. In this Review, the mechanisms of physical biocompatibility and chemical biocompatibility are discussed. In addition, other major research directions for achieving operational sustainability, including emerging power delivery and generation approaches, as well as wireless communications, are outlined. It can be envisaged that the future research advancements based on the outlooks presented in this Review can pave the way for a new nexus of connecting electronics with human bodies for enhanced healthcare.

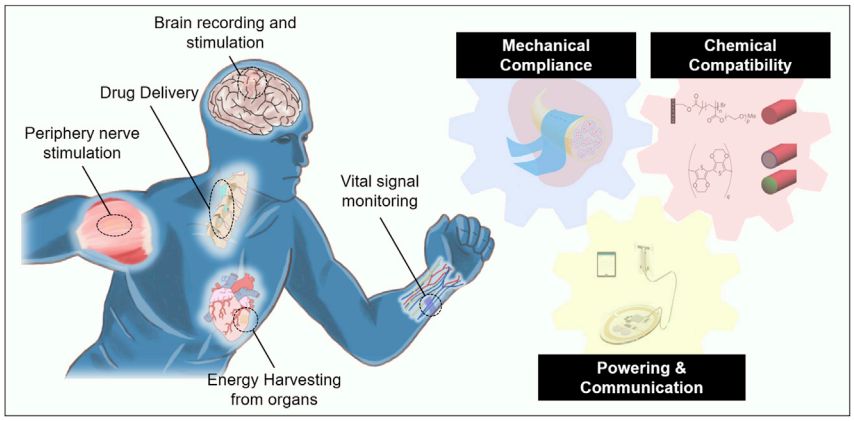

Figure 1. Representative functional components and major research directions of implantable bioelectronic devices toward long-term stability and sustainability

overall operational sustainability of implanted systems.[4] Data transmission represents another major challenge for making the devices fully enclosed in human bodies without the need for maintaining a transdermal cable connection, as an unhealed wound often results in reduced life quality for patients.[5]

Essentially, these challenges of interfacing electronics with biological systems originate from the extraordinary intricacy and delicacy of biological systems composed of soft, dynamic, three-dimensional (3D), vulnerable tissues. Moreover, animal/human bodies are guarded from external "invaders" by innate immunity, which works through a series of processes termed the foreign-body response (FBR),[6] to almost all types of implanted foreign materials.[7] Following the implantation, non-selective absorptions of proteins on the surfaces of implants will occur immediately. Host cells including neutrophils will enter the implantation site and generate cytokines, chemokines, and other enzymes to recruit monocytes, macrophages, and fibroblasts. The formation of foreign-body giant cells along with collagen deposition will eventually lead to the formation of a dense, avascular layer of fibrosis capsule around the implant, isolating it physically and physiologically from the host tissue. The presence of such electrically inactive fibrous encapsulation along the device surface will preclude the ionic and/or electrical communication between the electrodes and the target tissue. Thus, this cascade process typically causes both device failure and persistent inflammation in patients, which therefore stands as a prominent and common challenge faced by almost all types of implantable bioelectronic devices.[8] Based on immunology studies, the discrepancies in physical (i.e., mechanical and geometric) and chemical (i.e., wettability, charges, and the presence of certain immune-active functional groups) properties[9,10] at the electronics-tissue interface are two of the main aspects that determine the severity of the FBR.

As such, we reason that the ideal type of implantable bioelectronics for achieving stable and sustainable operations in human bodies should encompass the following characteristics: matched physical and chemical properties with tissues; the capability of sustainably obtaining or generating electrical power inside human bodies; and the function of wireless communication with external systems. Over the past decades, the developments of implantable bioelectronics have generated a major wave of material and device research for deeply integrating advanced functions with multi-aspect biocompatibility. In this regard, the major directions that have been established to date encompass soft (i.e., flexible and stretchable) electronics

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Table 1. Comparison of major physical properties of conventional Si electronics and biological tissues

	Conventional electronics	Biological tissues
Young's modulus	>100 GPa	1–100 kPa
Deformability (shown by strain)	<1%	10%–70%
Geometry	2D planar	3D curvilinear
Critical dimensions	a few millimeters[a]	1–100 μm

Data from Lacour et al.,[13] Prasad et al.,[14] and Fung.[15]
[a]Given as the size of individual integrated circuit chips.

for mimicking the mechanical properties of tissues, chemically biocompatible materials and devices, and implantable power-source technologies and wireless communication (summarized in Figure 1). In the following sections of this Review, based on the summary of the key design concepts and latest progress along each of these directions, we discuss the strengths and limitations provided by the major design strategies. To conclude, a projection toward the future research directions for this field is presented.

PHYSICAL COMPATIBILITY BETWEEN ELECTRONICS AND BIOLOGICAL SYSTEMS

Conventional electronics developed with Si and other inorganic functional materials have substantial mismatch with biological tissues/organs in physical form factors, including mechanical stiffness, deformability, size, and geometry, as compared in Table 1. These physical incompatibilities, as a whole, present major challenges not only for achieving high-fidelity functionalities but also for achieving long-term tissue-electronics compatibility. The planar geometry of electronics with the lack of deformability prevents them from achieving conformable interfaces with biological tissues for low-impedance and high-resolution signal transduction. According to immunology studies, significant mechanical and size mismatches between electronics and tissues typically lead to repeated tissue damage[11] and a more severe FBR.[12] On the other hand, the fragile nature of electronics renders them susceptible to possible mechanical damage from constant tissue/organ movements, which poses another limitation to the durability of the functions. The past 10 years have witnessed tremendous progress in creating new material and device-design concepts for electronics to minimize such physical mismatches with biological tissues.

Making electronics soft and deformable: from flexible to stretchable

When interfacing with biological tissues, the mechanical compatibility of electronic devices is characterized in two aspects: stiffness (i.e., the ease of deforming) and deformability (i.e., the maximum-extent of deforming). Almost all of the deformations from biological tissues can be demarcated into two basic types: out-of-plane bending and in-plane stretching. For bending, the stiffness, D, can be obtained from

$$D = \frac{Eh^3}{12(1-\nu^2)}, \qquad \text{(Equation 1)}$$

where E is the elastic modulus, h is the thickness of the material, and ν is Poisson's ratio.[13] The deformability of bending can be represented by the maximum bending curvature ρ_{max}, which is governed by the following relationship with the material's "strain-at-break" ε_{max}:

$$\rho_{max} = \frac{\varepsilon_{max}}{h}. \qquad \text{(Equation 2)}$$

On the other hand, for stretching, the stiffness follows the general relationship as

$$D = EhW, \quad \text{(Equation 3)}$$

where W is the width of the material. The deformability of stretching is simply determined by the material's strain-at-break ε_{max}.[16]

Such basic mechanical relationships tell us that the key parameters determining the mechanical properties of electronics encompass materials' Young's modulus E, strain-at-break ε_{max}, and feature sizes h and W. Therefore, the research efforts in the broad field of "soft electronics" have been mainly focused on the engineering of materials and devices from these three aspects. According to the basic deformation modes, the research to date mainly falls into two subfields: "flexible electronics" for increasing the capability of bending, mainly with thin plastic sheets serving as device substrates; and "stretchable electronics" for increasing the capability of uniaxial stretching, mainly with elastomeric films serving as devices substrates.

Flexible electronics

From the research efforts that started about 20 years ago, flexible electronics have achieved substantial developments and applications for interfacing with human bodies. Since the strain created by bending deformation can be engineered to be smaller than 1%, there are many choices of electronic materials that can be utilized for building flexible electronics.

Reducing the thickness of each component layer

For conventional inorganic electronic materials with strains-at-break typically below 5%, one universal strategy for enabling higher bending curvature, according to the mechanical Equation 2, is to reduce the layer thicknesses, which has been successfully realized in most of the inorganic electronic materials based on the recent developments in thin-film processing techniques and nanotechnology. Actually the conductor (usually metal) and dielectric layers in conventional electronics are often deposited as a thin film, readily with small thicknesses for achieving flexibility. As such, material engineering for thickness reduction is mainly needed for inorganic semiconductors, for which several major methodologies have been developed and successfully applied to a variety of materials. Semiconductors with layered structures (such as graphene, MoS_2, and $Sr_2Nb_3O_{10}$) or epitaxially grown thin films can be fabricated into free-standing nanomembranes or even atomic-thin layers through chemical or mechanical exfoliation methods.[17,18] Single-crystal Si nanomembranes/nanoribbons (Figure 2A) can be obtained through chemical etching on Si-on-insulator wafers.[19] Besides such two-dimensional (2D) thin layers, one-dimensional micro-/nanostructures (e.g., Si nanowires, carbon nanotubes, III-V nanowires) have also been obtained with a variety of semiconductors through either bottom-up synthesis or top-down etching methods. To further make such thin layers into devices, usually a physical transfer process for mounting them onto flexible polymer substrates is indispensable. Some of the inorganic-material-based flexible devices with state-of-the-art performances and significantly improved conformability to tissue/organ surfaces have been utilized for a number of bio-interfacing applications, including cardiac electrophysiology mapping,[20] brain electrophysiology mapping (Figure 2A),[21] and optogenetics-based brain activity modulation.[22] Compared with conventional rigid devices, these inorganic-material-based flexible devices bearing moderate bending curvatures can already offer an improved spatial resolution, higher signal-to-noise ratio, and better biocompatibility. However, their intrinsic differences in modulus and deformability with biological tissues still leave plenty of room for further improvements in physical biocompatibility.

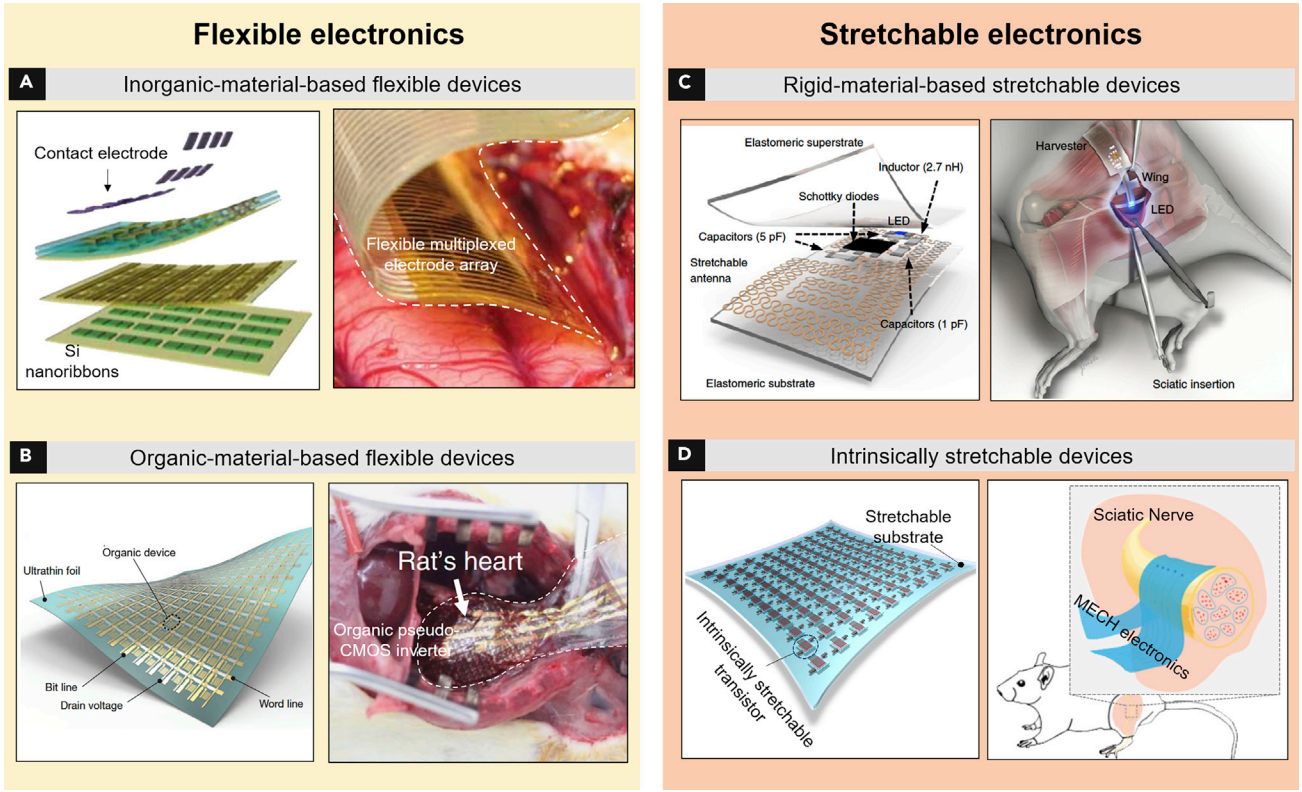

Figure 2. Flexible and stretchable electronics for achieving physical compatibility with biological systems

(A and B) Flexible electronics. (A) Inorganic-material-based flexible devices, as exemplified by the active matrix made from Si nanoribbons for cortex electrophysiological signal sensing. Reprinted from Viventi et al.,[21] with permission. Copyright 2011, Springer Nature Limited. (B) Organic-material-based flexible devices, as exemplified by the ultrathin organic pseudo-CMOS amplifier for cardiac potential mapping. Reprinted from Kaltenbrunner et al.[23] and Sekitani et al.,[24] with permission. Copyright 2013 and 2016, Springer Nature Limited.

(C and D) Stretchable electronics. (C) Rigid-material-based stretchable devices, as exemplified by the stretchable implantable optogenetic device. Reprinted from Park et al.,[25] with permission. Copyright 2015, Springer Nature Limited. (D) Intrinsically stretchable devices, as exemplified by the stretchable PEDOT:PSS hydrogel device for neural stimulation. Reprinted from Wang et al.[26] and Liu et al.,[27] with permission. Copyright 2018 and 2019, Springer Nature Limited.

Using softer functional materials: organic conductors and semiconductors

To further increase the achievable bending curvatures for flexible electronics, functional materials with higher strains-at-break are needed, as implied by Equation 2. The past 40 years have witnessed great developments in organic (and polymer) semiconductors and conductors with an electrical performance already approaching their inorganic counterparts.[28,29] Their softer and more deformable mechanical properties, e.g., with strains-at-break beyond 10%, make them uniquely advantageous for the development of soft electronics. While having them as thin-film layers in devices, the device can be further enhanced with regard to overall flexibility by thinning down the plastic substrate, which is represented by the so-called imperceptible electronics with the organic-semiconductor-based devices built on an ultrathin (~1 μm) polymer substrate, thereby achieving bending radii as low as 0.1 mm (Figure 2B, left).[23] The afforded advantage of high conformability has been demonstrated on *in vivo* cardiac signal recording and on-site amplification (Figure 2B, right),[24] as well as implantable power supplies.[30] The ultralow thickness and the limited uniaxial deformability also make such ultraflexible electronics highly vulnerable to in-plane deformations, which are ubiquitously generated by human bodies. Although the bending stiffness can be made very low from the ultrasmall thickness

on polymer-structured devices, whether the intrinsic modulus differences over three orders of magnitude between those flexible polymers and biological tissues will still cause prominent FBRs remains an important fundamental question to be studied.

Stretchable electronics

The development of "stretchable electronics" aiming to accommodate in-plane deformations from organs/tissues has attracted a substantial amount of research efforts and has made tremendous progress over the past 10 years. In general, compared with flexible electronics, stretchable electronics achieving rubber-like in-plane deformability need to endure much higher uniaxial strains (usually above 25%), which is much larger than what can be offered by conventional electronic materials such as Si. Currently, two general approaches have been established and significantly developed to create electronic materials and, hence, devices with sufficient stretchability: (1) geometric engineering on existing rigid electronic materials at different scales to enable stretchability; (2) development and utilization of new electronic materials with intrinsic stretchability.

Achieving stretchability from rigid functional materials

Given that stretchability is generally a requirement for electronic devices/systems to interface with biological systems, it becomes possible to use special geometric designs to circumvent the limitations of materials' rigid nature. This can be realized either by converting in-plane stretching into out-of-plane bending[31] or by taking advantage of layout heterogeneity in electronics to place strain mainly on the material components with higher stretchability.[32] The first approach comes from inspiration by a type of paper cut, "kirigami," which is a special cutting pattern enabling inherently rigid films to deform through bending and twisting of hinges and interconnections. This method can be applied to almost any rigid materials to achieve high stretchability by either using etching processes to create patterned cuts or generating microcracks from stretching on a strongly adhered elastomer substrate.[33] Besides these relatively sophisticated methods, a simpler approach is to enable out-of-plane buckling through in-plane compression of flexible sheets using a pre-stretched elastomeric substrate,[34] or film deposition onto the molded substrate.[35] In particular, this buckling concept has been successfully utilized in metal films for realizing stretchable conductors,[36] e.g., the "serpentine" designs of metal lines that achieve the stretchability beyond 100% strain.

The availability of stretchable conductors makes it possible, by engineering the local stiffness on an elastomer substrate, to dissipate the majority of the applied strain onto the interconnects, thus leaving the functional devices minimally stretched (Figure 2C left). From this generalizable design strategy, elemental devices are fabricated from rigid materials and commercial integrated circuit (IC) chips, which can be used to build electronic systems on stretchable substrates.[37] This approach serves to impart stretchability onto a variety of implantable devices such as a neurostimulator,[38] multi-functional cardiac monitoring platforms,[39] and optogenetic devices (Figure 2C).[25] Even certain data-processing functions are brought on board through the successful integration of Si chips. However, they typically result in low spatial resolutions, and the large thicknesses of these stretchable devices are not favored for enhancing the long-term biocompatibility and the interface conformability with tissues.

Imparting stretchability from the materials' level

To achieve intrinsic matching with biological tissues' mechanical properties in multiple aspects and across multiple length scales, a potentially more preferred

approach is to impart intrinsic stretchability onto all the component materials. Polymers that have loosely packed structures are the most promising family of materials for providing tissue-like stretchability. However, the semicrystalline structures of conducting polymers, as typically needed for efficient charge transport, limit the stretchability at 10% strain. As such, one of the key tasks in the development of intrinsically stretchable electronics is to resolve this paradox in packing structures for the concurrent achievement of high electrical performance and high stretchability.

So far, both chemical and physical approaches have been created to render rigid polymer conductors and semiconductors stretchable without sacrificing their electrical performance. For polymer conductors, e.g., poly(3,4-ethyl-enedioxythiophene) polystyrene sulfonate (PEDOT:PSS), several physical methods, such as adding plasticizers or solvent additives, or blending into a stretchable matrix, have been developed to largely improve the stretchability.[27,40,41] For polymer semiconductors, the developed strategies can be categorized into three major directions: backbone engineering, side-chain engineering, and morphological engineering.[42] In particular, the morphological engineering approaches, which are usually designed as a post-polymerization step, are proven to be facile, versatile, and highly effective. One representative example is to use a simple phase-separation process to form interconnected micro-/nanofibers from a conjugated polymer to afford the nanoconfinement effect that substantially improves the stretchability without affecting the semiconductor's electrical performance.[26,43,44] The other major challenge for creating intrinsically stretchable devices with high resolutions and reliable yields is the lack of fabrication processes compatible with polymers. The state-of-the-art progress up to now is a high-yield and broadly applicable fabrication process for intrinsically stretchable transistor arrays and circuits (Figure 2D, left), which could also be applied to the fabrication of other types of intrinsically stretchable devices for implantable applications.

With the expected advantages of enhanced biocompatibility and mechanical robustness, implantable devices with intrinsic stretchability have been demonstrated. For example, using PEDOT:PSS hydrogel with tissue-like stretchability and stiffness, neurostimulation (Figure 2D, right) and cardiac electrophysiological mapping devices have been created with relatively high resolution.[27] The high stretchability together with the hydrogel-afforded low modulus realized the conformable interfaces with tissues (i.e., nerves and heart) for low signal impedance and long-term biocompatibility. However, major challenges remain for further extending these benefits to more advanced implantable systems that incorporate transistors for multiplexing and on-site signal amplification. First, the achieved modulus of stretchable semiconductors and transistor devices are still orders of magnitude higher than that of the biotissues; second, the operation voltage needs to be significantly reduced to be compatible with biological systems; third, the chemical stability of polymer electronic materials/devices in a biofluidic environment demands systematic investigations and improvements.

CHEMICAL COMPATIBILITY BETWEEN ELECTRONICS AND BIOLOGICAL SYSTEMS

For implantable devices that are in close contact with the extracellular matrix (ECM), the chemical compatibility is usually one of the key factors that determine devices' usability and lifetime.[9,45] Overall, the chemical compatibility can be divided into three major aspects: materials' intrinsic toxicity, immunogenicity, and other influences on biological organisms (e.g., cell function). Traditional electronic materials,

including metals, Si, and other carbon-based materials, have been widely used for neural interface devices with relatively low toxicity; however, compared with certain polymers (e.g., poly(ethylene glycol) [PEG]), Si and carbon fibers are more susceptible to biofouling, thereby eliciting more severe tissue response.[46] The redox state of polypyrrole, a conducting polymer, has been found to influence the fibronectin conformation and affect cell attachment and growth.[47] These aspects exemplify the importance of synthetic materials' chemical properties in the biocompatibility of implantable devices.

Materials' toxicity

None or low toxicity is usually the foremost requirement for using a material for implanted devices, which is mainly determined by the material's chemical composition.[9] The mechanism of cell toxicity may include reactive oxygen species and oxidative stress, DNA damage, and mitochondrial dysfunction.[48] This aspect of biocompatibility is typically the first to be evaluated through *in vitro* cytotoxicity assays before a material can be brought into *in vivo* application.[49,50] Overall, a toxic material should always be avoided for utilization in implantable devices.

Materials' immunogenicity

Besides the toxicity, the materials' overall biocompatibility is also subject to interactions with the surrounding immune system.[51] In particular, immune-mediated FBR to implanted materials and devices has been a long-lasting issue for almost any chronic functions.[7] To conquer this challenge, reducing the materials' mechanical stiffness with the strategies discussed above has proved to be effective for suppressing the FBR. However, this is still not enough for full resolution of the issue. Further improvements have to come from the engineering of a material's chemical property so as to suppress part of the signaling pathways in immune responses.[45,52] Until now, the majority of the efforts on electronic materials and devices have been made via surface chemistry modification, either by coating with antifouling materials or by loading with anti-inflammatory drugs, which are both natural extensions from the research results on the non-electronic biomaterials (Figure 3A).[10,53]

Surface coating with antifouling motifs

As immune reactions to foreign materials are typically initiated from fouling of proteins and cells on the surfaces of implanted materials, surfaces resisting such processes, thus bearing antifouling properties, could effectively suppress the FBR.[56] Immunological studies of non-electronic biomaterials have suggested that antifouling properties can be obtained from materials with high hydrophilicity, as a dense hydration layer formed on the surface can resist protein absorption.[53] Therefore, a straightforward strategy to suppress the FBR is to coat a device's surface with a thin layer of antifouling materials. For the sake of keeping the electronic function, a primary requirement is to minimize the influence on the signal transmissions between device and tissue, for which a coating layer with ultralow thickness can help to a large extent. As an example, the grafting of PEG—a commonly used antifouling material[57]—on a carbon-fiber microelectrode for neural interfaces greatly suppressed FBR to a level much lower than that on unmodified Si probes (Figure 3B).[46]

To achieve further suppression of FBR, emerging types of antifouling materials, such as zwitterionic hydrogels with superhydrophilicity and therefore ultralow-biofouling materials, have been recently used as a replacement for PEG.[58] The zwitterionic polymer coating on a glucose sensor kept the surface free of dense collagenous capsule for at least 3 months after implantation (Figure 3C).[54] Despite these encouraging results from the surface-coating strategies, the influences on the transmission of different

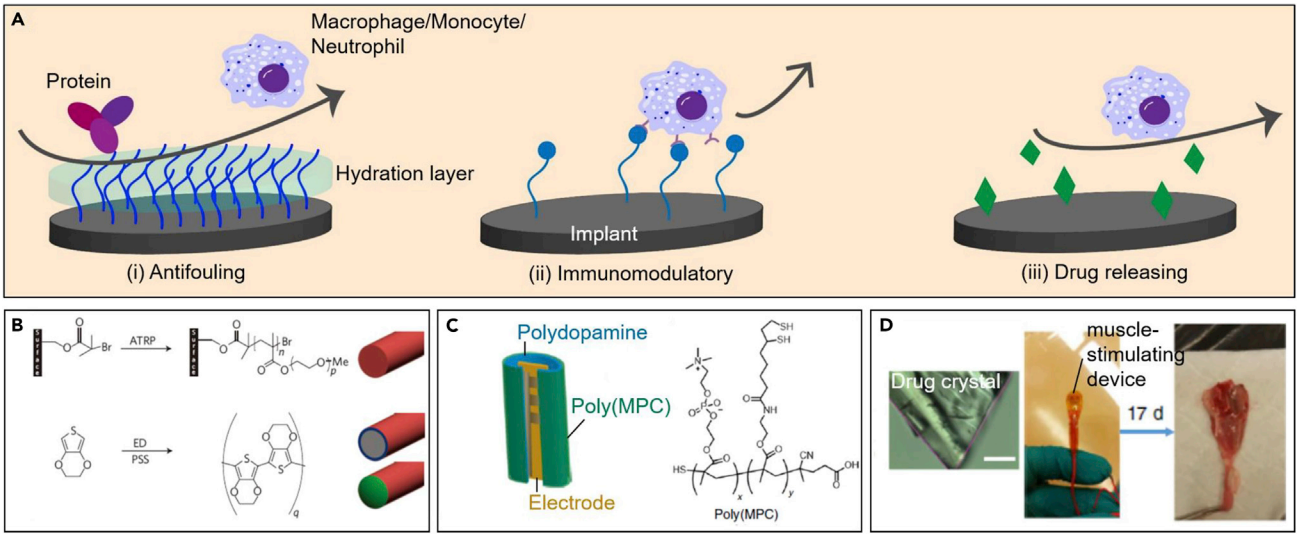

Figure 3. Approaches for suppressing the foreign-body response induced by implanted devices, which is mainly dictated by the chemical biocompatibility of electronic materials and devices

(A) Schematic illustration of the approaches taken to mitigate the foreign-body response (FBR), including: (i) the creation of antifouling surface through forming a hydration layer to resist protein absorption and subsequent fouling cells; (ii) the creation of immunomodulatory surface through small-molecule grafting to resist the absorption of fouling cells; (iii) the drug-releasing surface to dampen the FBR.

(B) PEG-grafted microelectrodes result in chronically implanted probes. Reprinted from Kozai et al.,[46] with permission. Copyright 2012, Springer Nature Limited.

(C) Zwitterionic hydrogels coated on glucose sensor reduce fibrosis and immune response. Reprinted from Xie et al.,[54] with permission. Copyright 2018, Springer Nature Limited.

(D) Gradual dissolution of GW2580 drug crystal on muscle-stimulating device reduces fibrosis. Reprinted from Farah et al.,[55] with permission. Copyright 2019, Springer Nature Limited.

types of signals at the device-tissue interfaces and the long-term stability remain to be investigated. To better avoid these limitations from the surface coating and potentially achieve even better immune compatibility, an underexplored but highly promising alternative is to impart the antifouling property onto electronic polymers as an intrinsic property through the engineering of their molecular and/or morphological structures. Of course, a primary requirement for the possible molecular engineering approach is to avoid affecting the polymers' electronic/photonic properties.

Loading anti-inflammatory drugs

Besides the passive strategies to suppress the first step—biofouling—in FBRs, research efforts have also been made to stop subsequent signaling pathways in the immune response cycles. A typical approach is to use anti-inflammatory drugs. Although there has been an established standard of using immunosuppressive agents to dampen the immune response, one key question is how to modulate only a specific immune population target without sacrificing the whole immune system. Moreover, to achieve long-term effectiveness, the dissolution of such drugs should be sustained for long time spans. Recently, it is reported that a crystallized drug formulation could specifically target monocyte-/macrophage-expressed colony-stimulating factor 1 receptor, and also features a slow dissolution rate and high drug density.[55,59] As a result, this strategy allows for an extended working lifetime of up to 6 months in non-human primates for suppressing FBR from a range of commercial medical devices such as CGM Enlite sensors (Figure 3D). However, the requirement on a pure crystal formulation for such continuous drug release places a limitation on applying it to other drug formulations. As such, new slow-release mechanisms are needed for the use of a wide range of anti-inflammatory drugs.[60,61]

Compared with the engineering of electronics' physical properties to improve biocompatibility, research efforts in the study and engineering of the chemical properties of electronic materials/devices remain much more limited. As most of the electronic materials have chemical structures that are very much dissimilar to the biological system, the interactions of these unique functional groups with biological systems need to be understood from the fundamental level. Moreover, since most cell membranes typically have a large number of receptors for receiving both chemical and mechanical cues, the influences of material and chemical properties should be intertwined with physical properties, which is another important aspect to be understood. Under the guidance of this fundamental knowledge, a substantial amount of research efforts and progress should be made in creating new material design principles for achieving long-term compatibility with biological systems. Moving toward functional devices and applications that have very different geometric heterogeneity and functional requirements (e.g., locations, signal types, duration of implantations), the suitability of each higher-level strategy (i.e., surface versus bulk, passive versus active) for improving the chemical compatibility should be systematically evaluated.

SUSTAINABLE POWER SUPPLIES FOR AND CONTINUOUS DATA ACQUISITION FROM IMPLANTABLE SYSTEMS

To achieve implantable systems with long-term sustainability and biocompatibility, the incorporation of power supplies and digital-computation units presents two significant challenges related to their intrinsic lifetime limit, bulky nature, and complexity in design and fabrication. The mainstays of the current approaches involve either leaving these components outside of the body with wired transdermal connection or implanting an unsustainable and/or non-biocompatible unit. Moving forward, innovations in materials and devices are highly desired to enable in-body power supplies with sustainable operations and implanted wireless data transmissions with long-term biocompatibility.

Implantable self-powered devices

Inside human bodies, the feasible choices for replenishing the power supply are either scavenging human-body energy or delivering energy wirelessly. For the option of energy harvesting, mechanical energy coming from all kinds of motions is the most universal and abundant energy resource in human bodies. The technologies for converting mechanical energy into electricity have been developed on the basis of various transduction mechanisms,[62] including electromagnetic induction, piezoelectricity, and triboelectricity. As an extension of the most mature approach for grid-scale electricity generation from mechanical energy, electromagnetic generators have been successfully miniaturized to harvest low frequencies of mechanical energy in implantable applications, with a typical output level of several microwatts. For instance, a wristwatch oscillation generator was devised to sustainably power a pacemaker.[63] However, the need for permanent magnets in electromagnetic generators poses a major challenge to achieving physical biocompatibility. As such, piezoelectric (Figure 4A) and triboelectric nanogenerators (Figure 4B), in which soft and low-dimension materials can be used, present as more promising candidates for implantable energy harvesting. Based on piezoelectricity, flexible and stretchable devices based on ZnO nanowires,[64] poly(vinylidene fluoride) thin film[65] and nanofibers,[66] and lead zirconate titanate ribbons[67] have been developed, which can be attached to organs such as the heart, diaphragm, and lung, with an output ranging from nanowatts to microwatts. Toward achieving better biocompatibility, the choice of materials is further broadened, to almost any type, in the more recently invented triboelectric nanogenerators, which

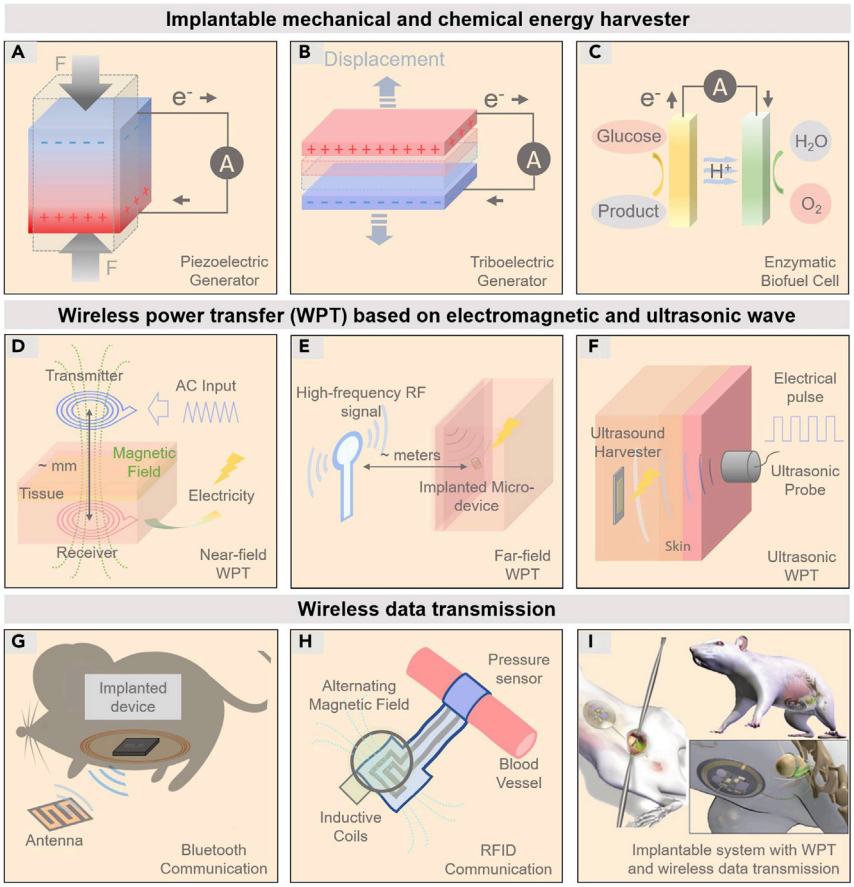

Figure 4. Energy harvesting and data transmission for implantable electronics

(A–C) Mechanisms of mechanical and chemical energy harvesting. (A) Piezoelectric-based mechanical energy harvesting. (B) Triboelectric-based mechanical energy harvester. (C) Enzymatic biofuel cell.

(D–F) Schematics for wireless energy harvesting from external power sources. (D) Near-field WPT. (E) Far-field WPT. (F) Ultrasound-based WPT.

(G–I) Schematics for wireless data transmission. (G) Bluetooth-based wireless communication. (H) Wireless capacitive pressure sensor based on RFID technology. (I) Implanted system with near-field WPT and Bluetooth-based wireless communication.

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derive from the universal existence of the triboelectric effect. As such, the materials utilized so far include stretchable elastomers (e.g., polydimethylsiloxane),[68] biodegradable polymers,[69] resorbable materials,[70] and self-healable materials.[71] With the generally high energy conversion efficiency, the output power of implantable triboelectric nanogenerators can reach up to tens of microwatts.[72] However, this is still insufficient for most of the sophisticated electronic functions. Additionally, much work remains to be done to improve the physicochemical biocompatibility through the development and use of novel materials while also enhancing the output power. Moreover, understanding the long-term influence of the energy-harvesting processes on the human body from a fundamental perspective is highly desirable in order to provide higher-level guidance on device designs.

An alternative energy-scavenging approach is biochemical energy harvesting by using biometabolites to generate electrical energy, which is realized by the device type of biofuel cells (BFCs) (Figure 4C). In implanted applications, BFCs are usually based

on enzyme-catalyzed redox reactions. For example, the enzymatic BFCs based on the glucose oxidation process can harvest energy from rats' blood with an output power of around tens to hundreds of $\mu W/cm^2$.[74,75] However, the output voltage of the enzymatic BFCs is normally lower than 1 V, which cannot directly be used to power the electronic devices. Although using a boosting circuit can help to mitigate this issue, new problems of complex circuitry and reduced conversion efficiency would arise. Furthermore, the *in vitro* and *in vivo* stability of enzymatic BFCs still remains to be adequately studied.[76]

Wireless power delivery

As the other general option for sustainably powering implanted devices, wireless power transfer (WPT) is primarily realized through the electromagnetic field and ultrasound waves. In general, electromagnetic power transmission can be categorized into two types according to the transmission distance: near-field and far-field (Figures 4D and 4E).[77] Based on electromagnetic inductive coupling between a pair of coils, the near-field WPT, e.g., the near-field communication (NFC), has been the most widely adopted method for powering implantable devices. Its prominent advantage is a high transmission efficiency greater than 80%,[78] which could therefore deliver a power output of milliwatts to implanted devices. To improve biocompatibility, a stretchable form factor has been imparted onto the coils.[25] However, the small transmission distance (i.e., a few millimeters) and the highly strict requirement of two-coil alignment limits the use of near-field WPT to subdermal devices.[79] Different from near-field WPT, far-field WPT operating at a higher frequency range (from high-megahertz to gigahertz) has larger transmission distances (up to several meters depending on the power of transmitter).[80] Nevertheless, the power transmission efficiency is usually low—far below 1%—so that the transmitted power is only in the range of microwatts. Some strategies have been devised to improve the transmission efficiency, e.g., through the use of a spatially focused magnetic field.[81] Even though electromagnetic-wave-based WPT is promising, systematic dosimetry study should also be conducted to guarantee its safety.[82] Aside from the electromagnetic-field-based WPT, an emerging approach of using acoustic waves to deliver power has been developed recently (Figure 4F), which could take advantage of the high power density (up to mW/cm^2) and deep penetration depth (up to 85 mm[83]) of the ultrasound wave into tissues. The received ultrasonic wave can be converted to electrical power through implanted mechanical energy harvesting, e.g., a piezoelectric or triboelectric nanogenerator.[84] Recently, an ultrasound WPT device based on a perfluoroalkoxy membrane and a gold film has been reported, giving nearly 100 μW of output power at the implantation depth of 5 mm.[85] Apparently, for the applications beyond subdermal devices, significant improvements are needed for the power output and the operation depth. Additionally, the possible health influences from ultrasonic wave exposure over long periods of time need to be carefully studied.

Common to all these different options for implanted powering, a power management circuit typically consisting of diodes, capacitors, and resistors is always an integral part of the power source. The power management circuit can regulate the generated or received electricity and help the power module to achieve an efficient energy-storage process. So far, despite the work on imparting biocompatibility onto energy harvester and transmission devices, the need to make such power management circuits biocompatible has been mostly overlooked.

Wireless data transmission

For wireless communications, extensively developed wireless communication technologies encompass Bluetooth and radiofrequency identification (RFID), including

NFC as a subcategory, which have been widely used in implantable systems. Generally, wireless communication modules consist of antennas, digital signal-processing units (ICs), and complex driving/matching circuits, all of which are conventionally built by Si electronics. In comparison, Bluetooth (Figure 4G) gives the largest signal transmission distance, up to 10 m, but needs sophisticated module design and a separate power source; RFID (including NFC) (Figure 4H) has much smaller transmission distance of only a few centimeters but can have the "tag" as the implanted part operating without a power source in relatively simple module designs. Regarding improved physical biocompatibility of the wireless modules, several promising strategies have been reported: miniaturizing the overall size of devices by compact 3D integration[86] and using NFC chips with a small package or even bare dies;[87] building the functional Bluetooth circuitry into a soft and stretchable format with stretchable interconnections (e.g., metal serpentine) (Figure 4I);[73] and using flexible or stretchable materials to fabricate the conformal antennas for RFID.[88,89] However, neither tissue-comparable mechanical modulus nor chemical biocompatibility has been achieved on wireless modules under implantation. The path of this overall target should be taken through the development of new material designs and device fabrications that can integrate intrinsic physicochemical biocompatibility with advanced electronic functionalities from the basic material to the IC level.

PERSPECTIVES ON FUTURE CHALLENGES

In this Review, we discussed recent progress in the development of implantable electronics toward the achievement of long-term stable and sustainable operations in human bodies. Despite remarkable advances in functional materials and devices for achieving multi-aspect physicochemical biocompatibility, sustainable power, and wireless data transmission, much progress remains to be made for ultimate integration of *in vivo* biocompatibility with sophisticated functionalities of biosignal acquisition, delivery, processing, transmission, and sustainable power, as well as minimally invasive implantation and removal capabilities. Here, we briefly summarize the main challenges.

1. Fundamental understandings of material/biology interfaces: As implanted materials' biocompatibility is jointly determined by the materials' multi-aspect physical and chemical properties, a set of clear understandings about the correlations of these properties and the biotissues' acute and chronic responses are the basis for setting the tangible development targets for implantable materials and devices. Although empirical knowledge and studies of non-functional biomaterials have provided some insights into the requirements of materials' physical and chemical properties, much still remains to be understood. For instance, what are the requirements of electronic polymers' molecular designs for achieving immune compatibility? What are the stiffness requirements on implanted devices across the micro- to macro-levels?
2. Biocompatible functional materials: Fully functional implanted systems are usually built with multiple types of devices using materials with a variety of functional properties including, but not limited to, conducting/semiconducting properties, electrochemical activities, electroluminescence properties, photoresponsivity, and memory properties. Therefore, the unique material designs for each of these functional properties need to be engineered to achieve the desired biocompatibility as endowed by several physical and chemical properties. Up to now, research progress has only been made on very limited types of functional properties for incorporating mostly a single-aspect biocompatible property, e.g., conducting/semiconducting properties

with mechanical stretchability. Many new material design concepts are waiting to be created to fill this material toolbox for biocompatible implanted electronics.

3. Functional device designs and fabrications using biocompatible materials: Devices made from emerging types of biocompatible materials can be expected to face new problems in achieving the most optimized device design for both functional performance and mechanical stability. Therefore, new device-design concepts could be needed. Moreover, toward realizing the functions with higher levels of complexity, e.g., wireless data transmission and onboard data processing that are usually based on a large number of transistors, innovations in device fabrications with the non-conventional types of materials should be continued for realizing adequately high device density, yield and performance uniformity, and large-area scalability.
4. Material and device properties enabling minimally invasive implantation and removal processes: Although the soft and deformable properties of electronics could be advantageous for enabling implantation surgeries with significantly reduced wound areas, new challenges arise from such soft form factors for achieving desired spatial accuracies. As such, new strategies are needed to solve this dilemma without having many sacrifices on either side. Moreover, for devices only providing temporal functions, the removal/clearing of these devices at the end of their functional life warrants a more autonomous process, such as stimulated degradation, rather than invasive surgery.
5. Power supplies with sustainability and biocompatibility: Although multiple technological options are available for potentially solving the challenge of recharging energy-storage power units that are under implantation, the achieved power outputs during implanted operations are generally insufficient for a variety of electronic applications. Future progress requires an in-depth understanding of each technology's suitability for different implantation locations and the improvements of material/device designs to concurrently provide high power efficiency and biocompatibility. Moreover, the long-term impacts of the energy-harvesting/delivery processes on the functions of biological systems should not be overlooked.
6. Encapsulations and long-term stability: As implantable electronics need to operate in biofluidic environments, encapsulation layers are indispensable for ensuring the functional stability of the devices. In general, materials for encapsulation layers are desired to have very low permeability for biofluids, chemical inertness, physical properties matching those of implanted devices, and good chemical compatibility with biological systems. For flexible electronics, as almost any materials can be utilized with reduced thickness, encapsulation can be made with densely packed materials, including both polymers (e.g., SU-8[90] and parylene[91]) and inorganic materials (e.g., SiO_2[26,43,44]). For stretchable electronics, encapsulations need to be made with elastomers, which generally have loosely packed structures and therefore relatively high permeability. So far, there has no demonstration of a satisfactory material with long-term sealing to stretchable devices, which requires research efforts and progress. Moreover, for functional materials, e.g., hydrogels and conducting polymers, which need to be exposed to biofluidic environments for the exchange of signals, new material designs are needed to improve their intrinsic stability against the issues of degradation, oxidation, and swelling.

Overall, we envision that the implantable electronics that can achieve the highest possible health affordability should encompass minimal invasiveness, multiple biocompatibility, wireless operation, and sustainable power supplies, which need

to be enabled by the innovations in material and device design. The future advent of such a new generation of bioelectronics will bring about a myriad of substantial advancements in precise disease-diagnosis capabilities, personalized and point-of-care treatments, restoration of lost functions, and a deepened understanding of human bodies, and even "cyborg" intelligence.

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AUTHOR CONTRIBUTIONS

All authors contributed to writing of the Review.

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