Review

Skin-Integrated Wearable Systems and Implantable Biosensors: A Comprehensive Review

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Abstract: Biosensors devices have attracted the attention of many researchers across the world. They have the capability to solve a large number of analytical problems and challenges. They are future ubiquitous devices for disease diagnosis, monitoring, treatment and health management. This review presents an overview of the biosensors field, highlighting the current research and development of bio-integrated and implanted biosensors. These devices are micro- and nano-fabricated, according to numerous techniques that are adapted in order to offer a suitable mechanical match of the biosensor to the surrounding tissue, and therefore decrease the body’s biological response. For this, most of the skin-integrated and implanted biosensors use a polymer layer as a versatile and flexible structural support, combined with a functional/active material, to generate, transmit and process the obtained signal. A few challenging issues of implantable biosensor devices, as well as strategies to overcome them, are also discussed in this review, including biological response, power supply, and data communication.

Keywords: biosensors; skin-integration; implantable; power supply; data communication

1. Introduction

All the manifested interest in biosensors started with the first invention of a glucose biosensor based on an oxygen electrode by Leland Clark in 1962 [1]. Since then, there have been many improvements and discoveries in the field. The concept of a biosensor is defined as a bio-analytical device, capable of providing specific quantitative and semi-quantitative analytical information by converting biological reactions or stimulus into measurable signals. Essentially, it comprises three essential components, a biological sensing component, connected to a detector or transducer component, and a signal processing system [2–4]. The biological element can be an antibody, a nucleic acid, an enzyme, a cell, or many others. A transducer depends on transduction methods, as electrochemical, optical, calorimetric or acoustic [2].

Biosensors have shown to be very helpful in our daily life and to play a relevant role in agriculture, food safety, homeland security, bioprocessing, environmental and industrial monitoring. However, biosensing in medicine is the most promising application of the field, since there is a need for new and improved devices with sensitivity, specificity, reliability and biocompatibility for the diagnosis,
monitoring and treatment of several health conditions. Additionally, to the troubleshooting, real-time monitoring and management of health problems, biosensors must also be able to simultaneously detect multiple analytes or stimulus, within biological fluids, outside and inside the body [2].

The demand for constant monitoring of vital signs aims to solve the issue related to the conventional need of hospitalization and supervision of the patient. Therefore, several studies have been made in researching and developing skin-integrated and implantable medical devices. In these devices, the most often monitored vital signs are heart electrical signals, blood pressure, pulse rate, blood glucose level, and respiration efficacy [5]. Advances in this field have provided freer patient motion and uninterrupted diagnostic data streams for medical monitoring [6].

In a biomedical context, biosensors need specific requirements, such as biocompatibility (sometimes, biodegradability and/or bioresorbability), miniaturization and reliability. Specifically, skin-integrated devices must be, in addition, flexible, stretchable, lightweight, and ultra-thin, allowing them to be able to conform and also to support all the constant motions of the skin in a non-discomforting way. Implantable devices also require all of those characteristics in order to not trigger or minimize any immune response and/or biofouling; to adapt to 3D organ’s shapes and to exclude the need of complex surgery. Nevertheless, there are some factors that limit the advances of this kind of implantable device and which are related to foreign body response (FBR), continuous and enough power supply that do not demand heavy and bulky batteries/electronics and data transmission without the need of wires.

All this progress in biosensors field has opened new routes to improve the medical care, diagnostic systems and the patient’s commodity.

The aim of this review is to give a brief overview in the biosensors field, exploring their types, function modes, and applications, with particular emphasis on the state-of-the-art of skin-like and implantable biosensors.

2. Biosensors Overview

A biosensor is an analytical device composed by a biological recognition element in direct spatial contact with a physical transduction element. Biosensors generally consist of three fundamental components: (i) the detector, to detect the stimulus or the biological component; (ii) the transducer, to permute the stimulus in an output signal; and (iii) the signal processing system, to process the output signal in an appropriate form. The proper combination of these three elements leads to a rapid and convenient conversion of the biological events to detectable and measurable signals [5,6].

These biological sensors can be broadly classified into different categories, based either on the sensing components or on the transducer components, as shown in Figure 1. Hence, on the basis of the different biological sensing elements, including enzymes, microbes, organelles, cells and biological tissues, biosensors can be categorized as catalytic biosensors, or affinity biosensors when including nucleic acids, antibodies or receptors. Generally, the biological recognition or sensing element consists of one of those mentioned biocomponents, immobilized in a transducer platform, able to detect the specific target analyte. The type of physiological change derived from the sensing event will set the transducing mechanism. According to the transduction component, biosensors can be grouped into electrochemical (conductimetric, amperometric, impedimetric and potentiometric) [7], optical (fluorescence, absorbance and chemiluminescence) [8], calorimetric [9] and acoustic [10].
2.1. Biosensors by Type of Bioreceptor: Catalytic and Affinity Biosensors

Bioreceptors are bond to the transducers surface, and are responsible for the specific binding of the analyte, as well as the physical-chemical mechanism that will originate the biosensor signal. Catalytic sensing is based on a catalyzed chemical conversion of the analyte from a non-measurable form to a detectible form. The progress of the biocatalysis can be monitored through a detection of the formation’s rate of a product, disappearance of a reactant, or the inhibition of the reaction [11–13]. Enzymes belong mostly to the group of proteins, with the exception of a small group of catalytic ribonucleic acid molecules. Glucose oxidase (GOD) is the enzyme most widely used in enzyme-based biosensors [11,14].

Affinity-based biosensors base their principle of action on the fact that stable and selective sensing complexes undergo important affinity interactions between the analyte and the immobilized biomolecule on the transduction element. The interactions occur through non-covalent binding of several functional groups in a short time, resulting in a measurable signal. These mentioned affinity complexes include antigen–antibody, DNA-oligonucleotides or protein–protein complexes [11,15]. A well-known affinity biosensor is the enzyme-linked immunosorbent assay (ELISA) [11]. This kind of biosensor is developed to improve association and diminish dissociations of target analytes. However, they easily become saturated and do not provide dynamic information about variations in the level of the analyte over time. So, as the binding may not be reversible, they cannot be regenerated and may not be applied for long-term analyte monitoring [11].

2.2. Biosensors by Type of Signal Transduction

The reaction between the analyte and bioreceptor causes some changes, such as release of heat, production of a new chemical, flow of electrons and changes in pH or mass, originating from a biochemical signal. To detect a small amount of this signal, the biorecognition event (e.g., chemical binding, micromechanical response, or a change in cell behavior) must be converted by the transducer into an electric signal, and amplified in order to be possible its quantification, display and comparison to estimated values [2,16,17]. There are a variety of transducer methods which are constantly being developed through the years for use in biosensors. The most common can be grouped into electrochemical, optical, acoustic and calorimetric.

An electrochemical transduction element can sense out, and use as a measuring parameter, some change in the electric properties derived from the production or consumption of ions or electrons of the biorecognition reactions. Typically, these reactions may either generate a measurable potential or charge accumulation (potentiometric biosensor), a measurable current (amperometric biosensor), a measurable conductance (conductimetric) or measuring resistive and capacitive changes (impedimetric biosensor) between electrodes. Electrochemical biosensors are commonly composed by...
three electrodes: a reference electrode, a working electrode and a counter electrode, although they can be composed by only two or more than three [16,18]. In electrochemical biosensors, signal-to-noise ratio is key for detection, especially in wearable and implantable systems where concomitant noise is significant [19,20].

Optical transducers use changes in optical properties resultant from the interaction between biorecognition elements with the target analyte at the transducer’s surface, including absorption, fluorescence, reflectance, emission or a change in an interferometric pattern. In other words, optical biotransducers collect information about an analyte through photons. Variations in concentration, mass or number of molecules are measured by a photodetector and, then, transformed into an electrical signal [2,16,21].

Calorimetric transducers measure variations of temperature caused by the biochemical reaction that happens when the target analyte binds the biorecognition element. The change in temperature can be related to the amount of reactants consumed or products formed, and measured using a thermistor or a thermopile [2].

Finally, acoustic transducers are based on either the bulk acoustic wave or the surface acoustic wave. Transduction is made through the detection of changes in their physiochemical properties as mass density, elastic, viscoelastic or electrical conduction properties, hence following a piezoelectric effect [16].

3. Biosensors in Medicine

Biosensors, as a fast-growing field by virtue of their ability to drastically help a number of analytical challenges and problems, have found applications in distinct areas, like agriculture and food safety, environmental monitoring, biotechnology, genetic engineering, pharmacology, defense, homeland security, industry, and essentially, in medicine and health care. In agricultural industry, biosensors are used for certain cases such as enzymes biosensors, to detect organophosphates and carbamates from pesticides, microbial biosensors for measurement of methane and ammonia, and bacteria-based biosensors for wastewater quality control. Regarding the food industry, biosensors are being used to measure amino acids, carbohydrates, inorganic ions, alcohols, acids, etc. [16,22,23].

Despite all the mentioned application areas, the most popular and with enormous potential is the application in medicine and biomedical diagnosis. This potential is driven by the need to solve medical and health problems including diabetes, cancer, chronic diseases such as heart disease, respiratory diseases, stroke, obesity, and so many others. Hence, measurements that are being established in health care are related to blood metabolites like glucose, lactate, and urea, and also to cancer biomarkers, folic acid, biotin, vitamin B12 and pantothenic acid [22].

The first introduction of a biosensor in medicine was in 1962, with the development of an amperometric enzyme electrode (platinum) for a glucose sensor by Leland C. Clark and Champ Lyons. These platinum electrodes detected oxygen as a result of the change on the enzymatic activity of the enzyme glucose oxidase which was entrapped with a dialysis membrane at the electrodes, depending on the surrounding concentration of oxygen [1,23]. Since then, glucose biosensors have so far been the most frequent, and many other biosensors have been developed for medicine, regarding improvements in the sensitivity, selectivity, and multiplexing capacity.

Lately, there is a growing interest in the application of biosensors in tissue engineering, notably in microfluidic tissue engineering models, since they can help sense specific biological molecules within the miniaturized tissue constructs in real-time, by means of ultrasensitive optical, electrochemical, or acoustic systems [16,24].

In medical and biomedical fields, biosensors must be very accurate, reliable, and should exhibit a high long-term stability with very little drift, and be resistant to the application of mechanical force, such as the ones generated by pulsatile blood flow [25,26]. Furthermore, implantable or wearable medical devices also need to be small, or otherwise they can be uncomfortable and bulky for the patient, especially when employed in confined volume areas, like blood vessels, lungs or the brain.
In addition, biosensors should not affect the measurement environment or patient’s well-being [27]. Although more challenging in terms of technology advances, both implantable and wearable devices, have in common the fact that they allow the collection of vital signals information (such as heart rate, respiration rate, skin temperature) and consequently, the monitoring of patients’ health over long periods of time.

3.1. Skin-Integrated Wearable Biosensors

A strategy to perfectly integrate electronics with the human body is the approach of skin-mounted epidermal electronics systems (EES) which provides a route to non-invasive continuous monitoring of clinically important physiological signals, such as skin temperature, heart rate, blood pressure, pulse and respiration rate, and transmits that information to the patient and the physician [25]. In addition to the assessment of these clinically relevant physiological parameters, sweat, saliva and tears also contain multiple physiology chemical constituents [26].

The use of this type of sensors holds considerable promise for maintaining and improving quality of life and consequently overrates the traditional systems. These traditional systems are known to possess wires or cables, point-contact electrodes affixed to the skin with adhesive pads, mechanical clamps or straps, or penetrating needles, mostly mediated by conductive gels. Besides that, they are also poorly suited for practical applications outside of clinical settings, because they can cause discomfort, irritation and inflammation to the user, lose adhesion over time, lack mobility, be generally very bulky due to their robust, plan and hard formats and components and only allow the monitoring of one physiological signal [25].

EES are skin-integrated stretchable devices, which are ultrathin, soft, low modulus, lightweight, and skin-like sheets, that can be intimately and physically mounted on the rough epidermis via van der Waals forces alone, without any mechanical fixation hardware or adhesive tapes. The EES with skin similar mechanical properties can act as a “secondary skin”. Thus, it can conformably adhere and laminate onto the surface of the skin by soft contact, in a way that is mechanically invisible and imperceptible to the patient, much like a temporary transfer tattoo. They also can be easily applied to any location on the patient’s skin [25,26,28]. At the end, they are natural interfaces capable to adapt and accommodate motions of the skin with no mechanical constraints, establishing a robust, non-irritating skin/electrode contact and allowing an intimate integration of diverse classes of electronic and sensor technologies directly with the body [29].

Considering that skin is the protective barrier between the internal body systems and the surrounding environment, every device that will be in contact with skin requires different design and fabrication principles, in order to mimic its particular mechanophysiological properties, and does not constrain or alter its natural motions or behaviors. Biocompatibility is also a requirement for this device, in order to avoid body-foreign response. Diverse electronic devices able of being flexible and stretchable have then been reported [26,30].

Flexible and stretchable electronic devices are usually built on substrates that reflect the flexibility and stretchability of the human skin, and subsequently these substrates are engineered using innumerable fabrication technologies, and material blends, in order to achieve the desired properties. Skin has a remarkably property of accommodating body movements concurrently to sensing functionalities, and thus needs exceptional flexibility and capability to stretch to ~30% strain. Skin-like flexibility provided to electronic devices can be achieved by using soft and flexible substrates and electronics, reducing the thickness of the substrate to lower the bending-induced strains, or arranging the active components of the device within the materials at a position that does not suffer strain during bending. Imparting stretchability involves two different strategies, such as engineering the shape of traditional (non-stretchable) electronic materials and the implementation of intrinsically stretchable components [31]. A strategic patterning of metallic components (metal, semiconductor and insulator) into optimized “horseshoe” or “serpentine” shapes allows the net to deform drastically, with little effect on its functionality [32].
Attaching epidermal devices to the skin can be accomplished through directly mounting the device onto a thin elastomeric supporting substrate or directly onto the skin [33]. This means that in the first approach the electronic components will be integrated firstly onto a stretchable substrate through printing techniques, following some 2D, such as discontinuous patterning and horseshoe or serpentine shapes; or even using 3D patterns, like ‘buckling’ a material by depositing a high-modulus material on a pre-stretched elastomer, followed by releasing the pre-strain, resulting in wave structures [34]. Following this type of integration, electronics can also be integrated directly, with a commercial temporary transfer tattoo as a substrate alternative to elastomeric materials [35]. The second approach is based on mounting the EES device directly onto the skin. This can be achieved either placing the EES on the surface of an elastomeric stamp and then transfer printing directly onto the skin, using a spray-on-bandage as an adhesive to facilitate the transferring and improve the robustness of integration; or either transferring the EES to a water soluble polymeric layer, e.g., PVA (poly(vinyl alcohol)), that will be further washed away after mounting on the skin, in order to leave only the EES. In this case, a layer of spray-on-bandage can also be applied [29,31].

Several skin-integrated devices have been developed in the past 10 years, either by mounting electronics onto a flexible substrate or directly onto the skin [33,35]. The first approach is more popular, and several reports can be found on the integration of electronics onto stretchable elastomers by 2D or 3D patterns. For example, Bao and his group produced transparent, stretchable and conducting single-walled carbon nanotubes (SWCNTs) films, by spray-depositing directly onto a substrate of poly(dimethylsiloxane) (PDMS) [36]. Chang and coworkers prepared a flexible pressure sensor using vertically aligned carbon nanotubes (VACNTs) supported by a PDMS matrix, which maintained their structural flexibility upon repeated compression (Figure 2a) [37]. PDMS is a common material to produce skin wearable flexible substrates, originating several types of sensors due to its chemical properties, biological compatibility, transparency, and good thermal stability, and especially its adhesion and non-adhesion areas that are clearly visible under UV light and can be easily adhered to the surface of electronic materials [38].

3.1.1. Sweat Sensors

Using sweat as a particular case of study, Khodagholy et al. showed a solid state electrolyte on a flexible transistor-based biosensor that can be used as a wearable bandage type sensor for detection of lactate [39]. Moreover, Koh et al. presented a collection of materials and device designs for soft, flexible, and stretchable microfluidic systems, including embodiments that integrate wireless communication electronics, which can intimately and robustly bond to the surface of the skin without chemical and mechanical irritation. This integration defines access points for a small set of sweat glands, such that perspiration spontaneously initiates routing of sweat through a microfluidic network and a set of reservoirs. Embedded chemical analyses respond in colorimetric fashion to markers such as chloride and hydronium ions, glucose, and lactate. Human studies demonstrated the functionality of this microfluidic device during fitness cycling in a controlled environment, and during long-distance bicycle racing in arid, outdoor conditions (Figure 2b) [40]. Finally, Xuan et al. reported a wearable graphene oxide (rGO)-based nanostructured composite working electrode deposited onto a flexible polyimide substrate for the electrochemical detection of glucose in human sweat when in close contact with human skin through a water-proof adhesive band [38]. Indeed, finding ways to capture and store the sweat in a controlled fashion is important for the further development of skin wearable biosensors. Some studies have reported hydrogels loaded with acetylcholine and iontophoretic induce local sweat accumulation for further analysis [41]. Alternative approaches rely on sudomotor axon reflex sweating produced via iontophoresis of a nicotinic agonist, using a wearable iontophoretic electrode [42,43].

3.1.2. Bio-Potential Sensors

Liang et al. reported the fabrication of transparent thin-films transistors that behave like an elastomer film by infiltrating a SWCNTs network and printing silver nanowires in an elastomeric
Kang et al. developed a system (Figure 2f) for the direct observation of glucose Raman peaks from in vivo pig’s skin. The experiments allowed a wide range of glucose concentrations and long integration times to obtain Raman spectra. The glucose concentrations were controlled through the injection of dextrose solution and insulin. Raman spectra were measured from the pig ears, with a high optical throughput Raman system confirming the presence of glucose and the linearity between its concentration and Raman peaks [44].

Son and coworkers presented a wearable bio-integrated system containing nanomembranes, as strain sensors and resistive random access memory (RRAM) array, a temperature sensor, and electroresistive heaters, heterogeneously fabricated and transfer-printed onto an elastomeric hydrocolloid patch, for monitoring movement disorders [45]. Nanomaterials such as SWCNTs, VACNTs, rGO, and nanomembranes are commonly used in wearable skin sensors, since they can highly improve the specific signal over the background noise characteristic of human fluids [46,47]. Moreover, for human motion monitoring, Wang et al. prepared a flexible and wearable strain sensor by adhering graphene woven fabrics on polymer and medical tape composite film, which proved to be molded around human skin without any irritation symptoms [48]. Miyamoto et al. demonstrated substrate-free electronics based on a conductive nanomesh structure, and showed the successful fabrication of inflammation-free, highly gas-permeable, ultrathin, lightweight and stretchable sensors that can be directly laminated onto human skin for long periods of time. Furthermore, a wireless system that can detect touch, temperature and pressure was successfully demonstrated using the nanomesh with excellent mechanical durability, and electromyogram recordings were successfully taken with minimal discomfort to the user [49].

3.1.3. Tattoo-Like Sensors

Finally, temporary tattoos represent quite attractive platforms for preparing body-compliant wearable devices capable of extracting good information from the epidermis [26]. Thus, bearing that in mind, reports of tattoo-like sensors started to emerge, using flexible substrates for electronic integration. Bandodkar and Wang group introduced tattoo-like electrochemical sensors, capable of mimic the epidermis and create a good adhesion to it, for the enzymatic amperometric biosensing of lactate in human perspiration (Figure 2c) [50] and glucose [51], or for the potentiometric biosensing of sweat pH (Figure 2d), [52] and ammonium [53]. Furthermore, they also developed a tattoo-based potentiometric sensor, coupled with a miniaturized wearable wireless transceiver, for the room temperature monitoring of sodium in the human perspiration [54]. Furthermore, Rogers group [25] established the concept ‘epidermal electronics’ by laminating devices onto the skin composed by sensors for temperature and strain and supporting electronics such as transistors, ring oscillators, diodes and radio frequency (RF) inductors in serpentine patterns.

The promising devices that use electronic integration directly on skin were demonstrated by Rogers group [29], that have figured out how to print multifunctional electronics right on the skin, without an elastomer backing using a rubber stamp to deliver the ultrathin mesh electronics. They also envisioned the use of a “spray-on-bandage” to add a thin protective layer and bond the system to the skin. The Bandodkar group used elastomeric stamps to print electrodes directly on human epidermis, associated to the use of wetting customized stamps with conductive inks pursued by contact. Current efforts and challenges reside in the miniaturization and integration of the electronic interface, data processing, wireless transmission of the results and the absence of re-calibration.

Therefore, with continued innovation, it is expected that skin-like devices will play a major role in the emergent body sensors for diverse applications [26].
Figure 2. Skin-integrated biosensor technologies. (a) Carbon nanotube-based pressure sensor for flexible electronics. (i) Photograph of vertically aligned carbon nanotubes (VACNTs) on a Si substrate; (ii) SEM images of VACNTs. The inset shows a high-magnification image highlighting the CNT alignment. (iii) Electrical resistance versus pressure for a VACNT block [37]. (b) A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. (i) Optical image of a fabricated device mounted on the forearm. (ii) FEA results of stress distribution associated with devices on phantom skin (PDMS) and respective optical images under various mechanical distortions: stretching at 30% strain, bending with 5 cm radius, and twisting [40]. (c) Electrochemical Tattoo for Real-Time Lactate Monitoring in Human Perspiration: monitoring of sweat lactate during 33 min of cycling exercise while changing the work intensity. (i) Exercise resistance profile on a stationary cycle. Subjects were asked to maintain a constant cycling rate, while the resistance was increased every 3 min for a total evaluation of 30 min. A 3-min cool down period followed the exercise. (ii) An “NE” lactate biosensor applied to a male volunteer’s deltoid; (iii and iv) Response of the LOx- (a) and enzyme-free (b) tattoo biosensors during the exercise regimen (shown in part i) using two representative subjects. Constant potential, +0.05 V (vs. Ag/AgCl); measurement intervals, 1 s [52]. (d) Tattoo-based potentiometric ion-selective sensors for epidermal pH monitoring. (e) Influence of repeated mechanical strain (stretching) upon the response of the tattoo ISE: (i) pH-responsive behavior of the ISE tattoo sensor prior to stretching (black) and following the 40th (red) stretch on GORE-TEX; one-unit pH decrement per addition. (ii) Images of the tattoo applied to the forearm at normal, during stretching, and after the 10th stretch [54]. (f) Raman spectroscopy system, actual probe setup with a subject, and glucose profile during experiment. (i) Schematic diagram of Raman spectroscopy system for in vivo animal (swine) skin measurement. (ii) Photograph of Raman probe setup. (iii) Glucose profile during the glucose clamping experiment [44].
3.2. Implantable Biosensors

An interesting and important application of biosensors is monitoring and measuring activity inside the human body. This kind of sensors are denominated as implantable biosensors when partially or fully introduced into the human body aiming to remain there for long periods of time in a minimally invasive way. Implantable devices are another viable alternative for a continuous monitoring, minimizing the pain and discomfort of the person.

In the near future, these implanted electronics will be an important tool in biomedicine, since it can provide a clearer picture of the cascade of events occurring inside the body in a certain period of time, helping monitoring chronic diseases, or progress after treatment and/or surgery. They can be found in the body, heart, eyes, blood and brain.

Implantable biosensors have several advantages over other monitoring devices, since they can monitor biological metabolites, nerve electrical stimulation, the detection of electric signals, restoring body functions, and be used for drug delivery, between others directly from inside the biological body [55]. A good example is monitoring blood pressure, an essential parameter in all organs of the human body. A change in the pressure may result in a deteriorating or injury of the physiological function. Hypertension and infarction are usual and serious health problems associated with the function or dysfunction of the cardiac muscle. Investigations of implantable and miniaturized blood pressure biosensors for continuous monitoring of hypertension and consequent efficient treatment are being made [56].

Developing a fully implantable biosensor requires the integration of heterogeneous elements, including electrodes for the recognition/sensing of the target analytes/vital signals, a circuit capable of performing measurements and transmitting the data, and a power source. The final shape and dimensions of the implantable biosensor must be biocompatible and well tolerated by the host, in order to avoid toxicity and chronic inflammation [57].

Hence, one of the highest obstacles on the development of implantable devices delays on the challenges associated with the mismatch between the hard, planar surfaces of semiconductor wafers and the soft, curvilinear tissues of biological systems. They tend to easily damage the surrounding tissues during insertion and exert chronic stress onto the adjacent biological environment, due to their sharp edges, stiffness, design and size [58,59]. So, clearly, conventional sensors, partially or fully rigid implants based on silicon wafer substrates, are more likely to be rejected and fouled. These materials are described as causing formation of fibrous capsules around the system diminishing the in vivo sensor performance, resulting in sensor failure [60–62]. Thus, for medical applications, it is mandatory to promote a replacement of silicon wafers by biocompatible, soft and flexible substrates, like biopolymer-based substrates, in order to alleviate that body-foreign issue and suppress fibrotic tissue encapsulation [56,60]. Commonly used polymeric substrates are polyethylene naphthalate, polyethylene terephthalate and polyimide [63]. These polymer substrates are essential for devices to overcome the mismatch between the hard, planar surfaces of semiconductor wafers and the soft, curvilinear tissues of biological systems [64,65].

Additionally, to achieve a particular home-based monitoring, implantable devices should be readily implanted and explanted in the body without the need of a complicated surgery. Under that circumstance, the implantable device must be extremely small, which demand unprecedented miniaturization of diverse functional components in order to fit in the implementation spot. If the biosensor is too large, there is required an incision surgery, if it is small enough to fit, it can be delivered by needle injection or via catheter [66]. These miniaturized biosensors implanted by needle-assistance were proved to induce less tissue damage, less inflammation and foreign body response by Kvist et al. [67]. Miniaturization is achieved through size reduction of sensing electrodes, driving electronics for power generation, data communication and their subsequent integration/packaging. Consequently, nanotechnology has been a potential and powerful avenue to accomplish components miniaturization and integration down to the micro and nanometer level, involving for example, photolithography, dip-pen nanolithography and micromachining techniques [60].
When the biosensor is implanted in the human body, there will be immediately biofouling; and a negative biological reaction as response to the foreign material itself known as FBR which are the mainly responsible for the functionality loss of the device, resultant from the tissue trauma/damage and poor biocompatibility of the sensor materials. According to many review articles, this negative response of the body can depend on the diverse properties of the biosensor, including shape, size, design, roughness, morphology and porosity, composition, interface material/device, sterilization, time of implantation, packaging and degradation [66,68].

The negative FBR of the body involves a cascade of events, including typical wound healing response, acute inflammation, chronic inflammation, and the formation of granulomatous tissue and eventually excessive fibrosis [69,70]. Firstly, when a tissue/device interface is created, the nonspecific blood and tissue fluids proteins adhere onto the surface or invade the materials. After that, it is the turn of inflammatory and immune cells, such as leukocytes, monocytes and platelets, to react and defend the body from the foreign object. These events are resultant from the acute phase, which may last between hours and days. Chronic inflammation happens when there is an incessant presence of the implantable device and thereby, continuous inflammation. In this phase, there is the action of macrophages, monocytes, and lymphocytes, as well as blood vessels proliferating and connective tissue restructuring the implant’s spot. The proliferation of blood vessels is important to wound healing and supply of needed nutrients. The granulation tissue will be eventually replaced by an extracellular matrix (ECM), which acts either as physical scaffold or an essential modulator of the biological events, like differentiation, regeneration, repair and tumor progression. FBR finish when there is a creation of a vascular, collagenous fibrous capsule around the implant that prevents the interaction of the implantable device with surrounding tissues [68,71]. Therefore, if an abiotic material is not well matched with the tissues and cells, and it is not biocompatible, the probability to remain in place long term; it is very low and could also result in an unsafe effect on the body [66].

To modulate these body responses that affect the in vivo functionality and longevity of implantable devices, several strategies have been reported [72–74], either passively via physicochemical features, or actively with molecules or matrix. These studies have essentially focused on the use of biocompatible material coatings, chemical surface modification of the device, conformable bioelectronics, steroidal and nonsteroidal anti-inflammatory drugs and angiogenic drugs [71,75].

Surface modifications can be achieved by changing the terminal chemistry of the device and by varying the roughness and surface topography. Functional groups, including hydroxyl, carboxyl, amine, sulfonate or phosphate groups, can be created on the surface, thus reducing the adsorption of some molecules. Probably, a single and simple surface modification alone will not be enough to provide biocompatibility. Imprinting micro- and nano-patterns on the device’s surfaces may mimic the natural topography of the ECM [71,75,76]. Yim et al. demonstrated that cells respond to the topography of substrates, in terms of adhesion, proliferation, migration, and gene expression [77].

3.2.1. Glucose Sensors

Several biocompatible materials, such as chitosan, alginate, cellulose, heparin and silk, have been employed as anti-fouling coating layers to act as a barrier against inner body elements such as cells, proteins, platelets, and chemical gases and still isolate the inner electrical and mechanical components. The coating membranes should maintain a desired and constant flux of permeation of analyte molecules over long periods of time; reduce protein adsorption; and promote the integration of the sensor with the surrounding tissues. They also must be thin and porous enough to allow the quick answer of the sensor to variations in analyte concentration. An example of one membrane with those characteristics was developed by Tripnis et al. [78], which consists of a layer-by-layer semipermeable membrane for amperometric glucose biosensors where the modification of the number of its bilayers, made possible the modulation of the diffusion of glucose toward the sensor. Another one was presented by Vallejo-Heligon et al. [79], that used a porous polyurethane coatings, and they concluded that when decreasing coating porosity increased sensor signal lag-time and attenuation (Figure 3a).
Xie et al. [80] demonstrated that coating a continuous glucose monitor sensor with a zwitterionic polymer, via a combinatorial-chemistry approach, significantly reduces signal noise, improving sensor performance, and significantly reduces the immune response to the sensor [80]. Zwitterionic polymers present ultra-low fouling properties and hinder non-specific protein adsorption, leading to reduced capsular formation when implanted [81]. However, some of the non-toxic biocompatible materials can eventually evoke a host immune response [60,76,82]. Tissue engineering approaches, based on the use of biocompatible hydrogels as extracellular matrices to recreate cell microenvironments and synergistically build and grow 3D tissue-like structures with embedded electronics, can be a parallel alternative to reduce the fibrotic tissue formation after implantation. Hydrogels have been engineered to recreate cell microenvironments to construct 3D tissue-like structures; due to their similarities in terms of high water content and physical properties, they resemble the extracellular environment of natural soft tissue [83,84]. The Papadimitrakopoulos group [82] studied a novel polymer coating based is also required on poly(lactic-co-glycolic) acid (PLGA) microspheres, dispersed in PVA hydrogels to prevent the FBR, and thus enhance sensor performance in vivo (Figure 3b). Means et al. [85] reported a membrane with an “actively antifouling” or “self-cleaning” mechanism to inhibit cellular attachment through continuous, cyclic deswelling/reswelling, in response to normal temperature fluctuations of the subcutaneous tissue. This thermo-responsive double network membrane is based on N-isopropylacrylamide (NIPAAm) and 2-acrylamido-2-methylpropane sulfonic acid (AMPS). After examining the FBR at 7, 30 and 90 days after implantation, the thermo-responsive membrane implants demonstrated a rapid healing response and a minimal fibrous capsule (~20–25 μm), which could be applied to extending the lifetime of sub-Q glucose biosensors [85].

Heo et al. developed a fluorescence-based sensor made of polyethylene glycol (PEG)-bonded polyacrylamide (PAM) hydrogel fibers, able to reduce inflammation when compared with PAM hydrogel fibers, which allows the continuous response to blood glucose concentration changes for up to 140 days. The implanted fiber remains at the implantation site and transmits fluorescent signals transdermally, according to glucose concentration, in blood, and can be easily removed to avoid potential side effects (Figure 4) [86].

Figure 3. Strategies for reducing foreign body response (FBR) in implantable biosensors. (a) Dexamethasone-releasing polyurethane coatings for glucose sensors. Micro-CT images of porous coatings created via the salt-leaching/gas-foaming technique with decreasing porogen fraction. The images show coatings of different morphologies created by varying the ammonium bicarbonate porogen concentration. (i) (ii) 90%, (iii) 60% and (iv) 30% [79]. (b) In vitro release profiles of poly(lactic-co-glycolic) acid (PLGA) microspheres and PLGA microsphere/PVA hydrogel composite coatings (n = 3 ± SD) at 37 °C, phosphate buffer solution in Polymeric “smart” coating for glucose sensors [82].
Yoon et al. developed a stainless-steel based non-enzymatic glucose sensor and a compact wireless continuous glucose monitoring system, through the modification of flexible stainless-steel (Figure 5). The flexible stainless-steel was highly effective in improving the adhesion between the metal layer and substrate. Authors monitored interstitial fluid (ISF) glucose values, at 5–15 min intervals, by subcutaneous implantation of the developed system. The comparison of the measured ISF glucose with blood glucose determined by the Clarke error grid analysis was performed, and revealed that 82.76% of the measured glucose was within zone A. The biocompatibility of the developed biosensor was proven by hematoxylin and eosin staining, and pro-inflammatory cytokines confirmation [87].

Figure 4. In vivo continuous glucose monitoring in mice using the implanted fibers. (a) Schematic illustration of the fluorescent hydrogel fiber designed for long-term in vivo glucose monitoring. (b) The fluorescent polyacrylamide (PAM) hydrogel fibers with and without polyethylene glycol (PEG) were implanted in mouse ears and remained in the mouse ears for one month. The fluorescence intensity of the fiber with PEG was observable through the ear skin for the entire month, whereas the fluorescence intensity of the fiber without PEG was barely detectable after one month. (c) Continuous glucose monitoring using implanted fibers and fluorescence intensity after implantation and after 140 days [86].

Figure 5. In vivo investigation of the developed non-enzymatic continuous glucose monitoring system. (a) Photograph of the developed non-enzymatic continuous glucose monitoring (CGM) and MiniMed CGM as a reference, which were implanted on a rabbit. (b) ISF glucose values measured using the MiniMed CGM (black line with square) and the developed non-enzymatic CGM (red line with circle) in animal experiment [87].
3.2.2. Bio-Potential Sensors

Conformable devices able to reduce the mechanical mismatches between the implant and the biological tissue have also been used as a strategy to overcome FBR in implantable biosensors [72]. For example, Wang et al. [88] reported on functionalized multi-walled carbon nanotubes twisted into helical fiber bundles that mimic the hierarchical structure of muscle and allow the monitoring of multiple disease biomarkers in vivo. The flexible fiber bundles are injectable, have a low bending stiffness and display ultralow stress under compression. When injected into tissue, the sensor formed a stable fiber-tissue interface and showed good biointegration, offering a robust tool for long-term sensing applications [88]. In another example, Bai et al. reported a silicon-based, bioresorbable photonic platform that relies on thin filaments of monocrystalline silicon encapsulated by polymers as flexible, transient optical waveguides for accurate light delivery and sensing at targeted sites in biological systems [89].

Another current method to control and/or minimize the body response is to incorporate bioactive molecules such as growth factors, anti-inflammatory mediators or drugs, to prevent the deposition of proteins on the surface of the device. The coupling of anti-inflammatory drugs to the device provides the release of the drug directly on the affected tissue [68,75]. Jayant et al. developed a system that can concurrently deliver 100% anti-inflammatory drugs (dexamethasone and diclofenac sodium) encapsulated in alginate microspheres, for use in implantable “Smart tattoo” biosensors to continuous glucose monitoring [90]. Coatings with combinations of three tissue response modifiers (TRMs): dexamethasone, VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) were prepared by the Papadimitrakapoulos group [91], in order to TRMs be delivered and prevent FBR and promote angiogenesis and blood vessel maturation around subcutaneous implants. Vallejo–Heligon et al. [92] investigated implanted glucose sensors coated with dexamethasone-loaded porous polyurethane coatings that combined angiogenic texturing with the local delivery of the anti-inflammatory agent to achieve the dual effect of curbing inflammation, and promoting the vascularization around indwelling sensors.

Regarding implantable biosensors and strategies to overcome FBR, it is also important to consider the sterilization of the material surface, before the implantation, concerning the elimination of harmful microorganisms through dry heat sterilization, pressured vapor sterilization, ethylene oxide sterilization, gamma radiation sterilization, and others [68].

3.3. Power Supply

One of the most critical challenges for the appropriate functioning of active implantable medical devices is the powering. The energy consumption of these devices is among microwatts to milliwatts. The power source is also a major contributor to the overall weight and size of the device, but with the advancements in MEMS (microelectromechanical systems) and nanotechnology, the electronic circuitry components have decreased dramatically [61,93,94].

Conventional implantable devices are usually powered by an external system, like bulky and heavy batteries which need replacement through surgeries because of the short service life, or by using direct transcutaneous wires which poses the risk of infections and may cause discomfort and restriction of movements to the patient [95,96]. Furthermore, conventional powering systems have limited utility due to discrepant contact with the crimped and curved surfaces of organs such as the heart, brain, eye, and lung [97]. Regarding that, and aiming to be long-lasting, autonomy, real-time monitoring, and implantable devices need an innovative power supply. Plus, applications in retinal and cochlear implants, deep brain stimulators for epilepsy and Parkinson’s disease, pacemakers and brain-machine, demand indwelling power sources, in order to allow implantable devices to work for several years in vivo with a limited power, and without any intervention or maintenance on the hardware [98]. As a consequence, several technologies have been investigated in order to improve these powering methods. Wireless powering is the most used method and is capable to yield high light power densities [99]. This approach has been focused on two wireless methods, far-field and near-field,
meaning the distance between the source and the device as a function of the powering frequency. Far-field is based on electromagnetic waves propagation captured at distances far from the source. Consequently, this type of powering is more relevant for devices located at greater distances, and when the power supply is not worn by the patient. Although, wireless implantable medical devices use near-field coupling since is a more efficient powering. This method uses inductive techniques and much lower frequencies to transfer and capture energy. To optimize these low frequencies, using energy harvesting technologies in terms of power conditions circuits becomes a critical task and technologies are emerging to face this drawback, like the use of triboelectric nanogenerators [100–102]. Near-field powering is a better fit for devices that require high power consumption and with non-relevant size, like sophisticated closed-loop neural prostheses [88]. However, these two wireless powering methods have restraints, since the impedances of the both transmitting and receiving coils are sensitive to the distance and the orientation between them, likewise the electrical properties of the bio-tissues between the coils [99,103].

For the extreme miniaturization of devices that aim to be implanted in deep tissue spaces, Ho et al. demonstrated a method that can overcome those near-field and far-field limitations. The method is based on a termed midfield powering, to create a high-energy density region deep in tissue, inside of which the power-harvesting structure can be made extremely small. This method will enable the possibility of new generations of implantable systems that can be integrated into the body at minimal cost and risk [104]. However, Jiang et al. have suggested a novel low-frequency wireless power transfer technology using rotating rare-earth permanent magnets that are suitable for the near-field wireless power transfer to biomedical implants [103]. Moreover, Bakula et al. successfully demonstrated the combination of multiple requirements, such as low power, small size, power and frequency adaptability in one implant control system, based on a Royer oscillator with RF and near-field communication links [105]. He et al. proposed a wireless power supply based on a MEMS-based ultrasonic transducer with piezoelectric thick film [106]. Finally, Shon et al. developed an implantable wireless neural interface system for simultaneous neural signal recording and stimulation using a single cuff electrode (Figure 6a). The system also includes a wireless power consortium-compliant power transmission circuit and a medical implant communication service-band-based radio link. The maximum reliable operating distance for wireless power transmission was, approximately, 11 mm, and the overall efficiency corresponded to 67%, which is higher than conventional wireless power transmission devices [107].

Another interesting method is to harvest the energy of physiological processes or the body’s biomechanical motions, including vibration due to the movement of the patient, vibrational energy of breathing, cardiac/lung motions, muscle contraction/relaxation or blood circulation. Implantable devices powered by harvested energy have longer lifetimes and afford more comfort and safety than conventional devices. Thus, this method can be attained to battery-less implants, where is possible to directly power the device through the harvested energy from natural or artificial power sources surrounding the patient [61]. Different human body activities are sources of kinetic and thermal energies, and consequently producers of different levels of power. Kinetic energy harvesting bases on collect energy associated to human motions and converts it into electrical energy through piezoelectric, magnetic induction generator and electrostatic transduction methods [108]. Hwang et al. introduced a flexible and high-performance piezoelectric energy harvester enabled by a single crystalline PIMNT (indium modified crystalline Pb(In1/2Nb1/2)O3-Pb(Mg1/3Nb2/3)O3-PbTiO3) thin film on a PET (polyethyleneterephthalate) substrate (Figure 6b), which used mechanical deformation and biomechanical motion [109]. Park et al. fabricated a highly-efficient, flexible, lightweight, and large-area piezoelectric PZT thin film nanogenerator on PET substrate [110]. Shin et al. demonstrated high-performance flexible piezoelectric nanogenerators based on a composite thin film composed of hemispherically aggregated BTO nanoparticles and p(VDF-HFP) [111]. Karker et al. presented a plasmonic-based energy harvesting from chemical sensors where thermal energy is harvested using lithographically patterned golden nanorods [112]. Biocells are also power sources that
can be employed in the human body, implementing biological analytes as catalysts at the anode and
and cathode. They are capable of mimicking many of the metabolic pathways, thus extracting electrical
energy from energy sources naturally found in biological fluids [113]. Ghosh et al. developed a
self-powered wearable bio-inspired piezoelectric biosensor, based on collagen nano-fibrils, which could
transduce the minute deformation of human skin. The developed energy harvester acts as a sensor
that interacts with human body parts to monitor real-time physiological signal, such as, arterial pulses,
vocal cord vibration and gentle wrist movements [114].

**Figure 6.** Power supply strategies for implantable biosensors. (a) Sensor implantation: (i) cuff electrodes
wrapped around the tibial and peroneal nerves and (ii) implantable device inserted under the back
skin of a rabbit [107]. (b) Deep brain stimulation (DBS) applications using the flexible indium modified
crystalline Pb(In1/2Nb1/2)O3-Pb(Mg1/3Nb2/3)O3-PbTiO3 (PIMNT) energy harvester and characteristics
of the flexible PIMNT film (i) a schematic illustration of DBS applications using the flexible PIMNT thin
film energy harvester and (ii) a photograph of the final flexible PIMNT harvesting device completely
bent by human fingers [109].

Du Toit and Lorenzo reported two innovative constant flow enzymatic biofuel cell configurations
that employ highly porous gold electrodes and glucose oxidase and laccase as the catalysts providing
that way continuous power generation [115]. Zebda et al. described an original design of a glucose
biofuel cell, based on carbon nanotube/enzyme electrodes, which had a successful implantation in
a rat and produced significant levels of energy at a single location [116]. Dong et al. focused on
providing power for implantable medical devices using a microbial fuel cell implanted in human
transverse colon [93]. More recently, Wu et al. developed a wireless implantable sensor prototype
with subcutaneous solar energy harvesting. This system is based on a power management circuit,
a temperature sensor, and a Bluetooth low energy module. The results shown that the solar sensor
can output tens of microWatts to a few milliWatts, depending on the light conditions and in the
implantation zone, being the most accurate between the neck and shoulder [117].

In general, to develop energy harvesting methods, it is expected that electronic technology
continues its evolution of decreasing energy consumption. Harvesting techniques and their application
are in constant expansion and are becoming more attractive.

### 3.4. Data Communication

Post implant monitoring is an essential factor for the implantable devices and patient care. Remote
monitoring fills the gap of the lack of information resultant from the conventional follow-up visits,
providing large prospective trials, automatic daily transmissions and long-term support at a distance,
allowing the patient to be at home [118].

Advances on implantable medical devices are demanding, since the methods to translate the
follow-up observations are time consuming and complex. Better methods to transmit the collected
data obtained are urging for further developments in implantable devices. A considerable increasing
in the density of analysis and interpretation/processing algorithms is also required [61]. The devices
are equipped with a micro-antenna for communication and thereby the sensed data are remotely
transmitted to an external system, such as a computer, smartphone or tablet and network, like wireless
body area networks (WBAN). The antenna may be built up by flexible materials and consequently,
flexible coils, to improve the biocompatibility and conform to the inner body and organs.
Various developments of data transmission have occurred over time, starting from fax reports to a social networking service system, from wired system to wireless communication, and from one-direction transmission to bidirectional transmission [119]. Since wires are related to surgical complications due to their probability to break, become infected or introduce electrical noise in the recording by motion artifacts or by antenna effects, wireless communications have emerged to avoid those complications [120]. Wireless communication can be achieved by using radio frequency (RF), optical, sound, or infrared media, although RF is the most common [121]. Wireless RF telemetry also depends upon a considerable power and can experience poor transmission through biological tissue. Wireless data transmissions through electromagnetic induction, or light were developed, but they have troubles transmitting the data when the external data transmission unit alters from its proper position; therefore, other methods are being developed [122]. The community for medical devices normally assigns specific bands for the wireless communication of implantable devices, such as a very high frequency band at 174–216 MHz, an ultrahigh frequency bands at 401–406 MHz and 450–470 MHz, and other narrow bands within the industrial, scientific and medical bands of 6.765 MHz to 245 GHz [121]. A recently wireless communication employed to transmit signals is the intrabody communication, which uses the conductive properties of the body. In this case, signals can be transmitted from the implanted device, either to electrodes mounted on the skin or to receiver electrodes also implanted inside the body. This implanted receiver can be connected to external equipment using wireless RF telemetry. In this way, less power is required to transmit to the implanted receiver electrodes [120]. Nevertheless, inductive method communication is the most applied in applications where the sensor element is implanted deeper into the body [56].

Asgari et al. integrated an antenna, a transceiver unit and a wireless network algorithm to enable their left ventricular assistance devices to establish a reliable telemetry communication with an extracorporeal platform, such as a smartphone, tablet or personal computer [123]. Kilinc et al. presented a system for wireless power transfer and data communication of battery less biosensor systems implantable in small animals, based on an implant coil placed to induce AC voltage from the available magnetic field [124]. Ryoo et al. developed an endoscopically implantable biosensor for real time detection of UGIB equipped with a radio and antenna capable of transmitting out of the body and wirelessly linked to an external computer and transceiver [125]. Aldaoud et al. implemented a miniaturized wireless blood pressure sensor interface which used capacitive coupling to transmit the sensed data, as well as wireless inductive powering [126]. Olivo et al. tested by micro-fabrication high-thickness spiral inductors for the remote powering of implantable biosensors through inductive link. These inductors enabled bidirectional data communication with the external transmitter [127]. Luo et al. successfully designed and microfabricated a RF wireless LC resonant pressure sensor completely made of biodegradable materials. Here, an inductor coil acts not only as an essential component of the resonant sensor, but also gives routes for magnetically coupling the sensor to a coil outside the body [128].

Additionally, to have an accurately reading, analysis and monitoring of signals from the human body, there is a requirement of sensitive transducers, filter and amplification units [129].

Lee et al. developed an implantable device to sense electrocardiogram signal, but also the voltage level of the secondary cell and temperature inside the implantable device, being the data transmitted, by RF link, to a PC program or a mobile application. Of the several frequency bands, the medical device radio communication service has been allocated in the 401–406 MHz for data transmission [130]. Mulberry et al. developed a CMOS (complementary metal–oxide–semiconductor) chip mounted into a polyimide flexible printed circuit board for a neural recording implant (Figure 7a); this flexible substrate enables the system’s wireless power transfer by using spiral traces as an inductive coil. Additionally, it holds a system-on-chip (SOC) that operates the CMOS chip (Figure 7b) and sends data wirelessly via Bluetooth low energy (BLE) to a computer. The SOC contains an ARM microcontroller, which generates the required timing signals to operate the CMOS neural chip and processes and packages the data it receives to send via BLE [131].
More recently, Vennemann et al. developed an implantable magnetic blood flow sensor (Figure 7c), being the wirelessly transmitted to the patient’s smartphone for in-depth processing. The wireless operation could be sustained as long as an NFC (near field communication)-enabled smartphone is in the vicinity of the implant and transmitting power through inductive coupling [132].

Figure 7. Data transmission strategies for implantable biosensors. (a) The implantable sensor small size is achieved by the use of wireless power transfer provided by an external coil and the flexible substrate. The device transmits data via a low energy Bluetooth link to a receiving device; (b) Photos of the implantable neural interface: (i) the neural interface being flexed by a hand, (ii) the top side of the neural interface, (iii) the bottom side of the neural interface [131] and (c) illustration of the heart valve monitoring system, which communicates the data by wireless [132].

3.5. Fabrication Methods and Current Applications

Essentially, remarkable advances in implantable biosensors have been achieved through the use of the combination of electrical active matrices on flexible polymeric substrates. To make them so potential and multifunctional, various fabrication methods are currently available [133]. Microfabrication methodology includes several processes used in the fabrication of semiconductors and integrated systems. Among these processes, photolithography, deposition techniques, doping and etching stand out. Over the past years, this technology extended also for the development of small-scale miniaturized devices, and it has been extensively applied to fabricate micro-engineering surfaces, sensors and transistors, MEMS, micro-opto-electro-mechanical systems (MOEMS), and also in the fabrication of flexible and stretchable devices [134]. For example, Theodor et al. reported a sensor system for the continuous monitoring of blood pressure using an acceleration sensor implanted on an artery using minimally invasive techniques. The sensor system is based on a flexible polyimide substrate with photolithographically structured copper tracks glued by thin layers of epoxy adhesive to both sides of the polyimide substrate. A surrounding polyimide layer covers and electrically isolates the copper tracks. Mounting of the electronics to the substrate is performed by opening of the insulating layer and reflow soldering. A surrounding layer of biocompatible parylene-C is deposited and protects the circuit from body fluids and the organism from ions of the circuit (Figure 8a) [135]. Table 1 shows several examples of current applications in the field of implantable devices, with respective materials and the common features of fabrication technologies. Regarding the exposed information on the table, the most frequent methods are related to conventional micromachining technologies, such as chemical vapor deposition (CVD), physical vapor deposition ((PVD)—evaporation and sputtering), etching and reactive ion etching (RIE), thermal oxidation. Besides those, there is also the presence of printing methods, essentially screen and transfer printing. For example, Viventi at al. report the development of a class of mechanically flexible silicon electronics for the multiplexed measurement of signals in an
intimate, conformal integrated mode on the dynamic, three-dimensional surfaces of soft tissues in the human body. The fabrication consisted of doped single crystal silicon nanoribbons on a silicon wafer that are transfer-printed to a thin plastic sheet. The deposition and patterning of suitable dielectric and metal layers complete the functional electronics, and specialized designs and multilayer encapsulation schemes protect all active components from the tissue and surrounding biofluids (Figure 8b) [136].

![Figure 8](image_url)

**Figure 8.** Fabrication techniques of implantable biosensors. (a) Structure of the polyamide foil with Cu tracks, mounted sensor and encapsulation in Implantable accelerometer system for the determination of blood pressure [135]. (b) Schematic illustrations and images of steps for fabricating active, conformal electronics for cardiac electrophysiology. (i) Schematic illustration (left) and optical micrograph (right) of a collection of doped silicon nanomembranes in a unit cell. (ii) Configuration after fabrication of the source, drain, and gate contacts, with suitable interconnects and row electrodes for multiplexed addressing. (iii) Configuration after fabrication of the second metal layer, including the column output electrodes. (iv) Final layout after deposition of encapsulation layers and fabrication of the tissue-contacting electrode [136].

Patterning electronics materials on diverse flexible substrates through printing technologies has received greater attractions. Usually, there are two major approaches of printing system; contact and non-contact printing. In contact printing, as the name says, there is a physical contact between patterned structures having inked surfaces, with the substrate. This process includes nano-imprinting, transfer printing, micro-contact printing technologies, and others. By contrast, in a non-contact approach, the solution is poured through openings or nozzles, and by moving the substrate holder in pre-programmed pattern, structures can be obtained. In this one, techniques like screen printing, inkjet printing and slot-die printing can be attributed [137]. For example, Viventi et al. developed new devices that integrate ultrathin and flexible silicon nanomembrane transistors into the electrode array, enabling new dense arrays of thousands of amplified and multiplexed sensors that are connected using fewer wires to record and stimulate the brain. These devices were fabricate using a multi-layer process, where doped silicon nanomembranes, structured into ribbons, were located in the first layer through the use of transfer printing technology [138]. In another example, Kim and Viventi et al. reported a material strategy for a type of bio-interfaced system that relies on ultrathin electronics supported by bioresorbable substrates of silk fibroin. For this, commercial polyamide films were attached to a temporary carrier substrate consisting of a glass slide coated with PDMS. Then, electron beam evaporation formed uniform coatings of metal (Cr/Au, 50/1450 A). Photolithography and patterned etching yielded arrays of interconnect lines. Thin layers of polyamide were spin-cast and patterned by reactive ion etching left only the ends of the lines exposed. Further deposition and patterning defined square metal electrode pads at these locations. Peeling these away from the PDMS-coated glass slide and bonding them to an ACF cable completed the fabrication [139].
Table 1. Summary of applications and fabrication methods of implantable devices.

| Category                  | Location          | Feature/Function            | Active Layer                          | Supporting Layer                  | Fabrication Method                        | Reference |
|---------------------------|-------------------|-----------------------------|---------------------------------------|-----------------------------------|-------------------------------------------|-----------|
| Implantable Biosensors    | Heart             | Mapping cardiac electrophysiology | Si-based circuits                     | PI (substrate and dielectric layer) Epoxy (dielectric layer) | Transfer Printing | [136] |
|                           |                   | Harvesting mechanical energy from cardiac motions | PZT (capacitor) Au interconnections | PI (substrate)                      | Litography/ Etching/ Transfer Printing | [140] |
|                           |                   | Cardiac electrophysiological mapping | Cr/Au electrodes (rectangular, serpentine shapes) | PDMS                          | Photolitography/Etching/ Transfer Printing | [141] |
|                           |                   | Electrical cardiac mapping | Cr/Au interconnects (serpentine shape) | Silk (dissolvable substrate)       | E-beam evaporation/Photolithography/ Etching/Transfer Printing | [65] |
|                           |                   | Thermal activity            | Pt (resistors) Ti/Pt (sensors) Cr/Au interconnects (serpentine shape) | Silk (dissolvable substrate)       | E-beam evaporation/Photolithography/ Transfer Printing | [65] |
|                           | Carotid artery    | Monitoring of blood pressure | Cu electrodes                          | PI substrate                      | Photolithography                          | [135] |
|                           |                   | Mapping brain signals       | Au electrode patterns                  | PI (mesh) Silk (dissolvable substrate) | Photolithography/Etching                 | [139] |
|                           |                   | Mapping neuronal activity   | Pt electrodes (contact) Au electrode (base) | PI (substrate)                   | E-beam Evaporation/ CVD/Transfer Printing | [136] |
|                           |                   | Neuronal imaging; optogenetic | Graphene Au connection pads            | Parylene C                        | CVD/E-beam evaporation/RIE               | [142] |
|                           | Brain             | Brain-machine interface; spinal neuromodulation | Au interconnects Pt electrodes        | Silicone                          | Photolithography/ Screen-Printing/Thermal evaporation | [143] |
|                           |                   | Chemical agent delivery; Glutamate sensing | Pt electrodes                         | PDMS                             | Photolithography/E-beam evaporation/ Etching | [144] |
|                           |                   | Quantification of pH and O$_2$ | Multi-walled carbon nanotube           | Carbon nanotube fibers            | CVD                                       | [145] |
|                           |                   | Monitoring of dopamine      | Ethylenedioxithiophene tailored with zwitterionic phosphorylcholine | Carbon fiber                      | Electropolymerization                     | [146] |
|                           | Eye               | Retinal stimulation         | Boron doped diamond electrodes         | PI (substrate) SiO$_2$ (sacrificial layer) | CVD/Etching                             | [147] |
| Category                | Location                        | Feature/Function                     | Active Layer                                   | Supporting Layer                     | Fabrication Method  | Reference |
|-------------------------|---------------------------------|--------------------------------------|-----------------------------------------------|--------------------------------------|---------------------|-----------|
| Skeletal muscles; skin; |                                 | Electrical activity measurement      | Si and GaAr (serpentine shape)                | Modified silicone (substrate) PVA (temporary support) |                     | [25]      |
| heart; brain            |                                 |                                      |                                               |                                      |                     |           |
|                        | Bovine haptoglobin measurement  | Gold nanoparticles Multi-walled      |                                               | Paper                                | Printing            | [148]     |
|                        |                                 | carbon nanotube                      |                                               |                                      |                     |           |
| Subdermal dorsal region |                                 | Thermal therapy                      | Mg (conductors) MgO (dielectrics) Si         | Silk (dissolvable substrate)         | Transfer Printing/PVD | [58]      |
|                        |                                 | nanomembranes (semiconductors)       |                                               |                                      |                     |           |
| Peripheral nerve        |                                 | Glucose sensor for inflammation     | Pt (working electrode) Ag/AgCl (reference    | PI substrate               | RIE/Sputtering/   | [149]     |
|                        |                                 | monitoring                           | electrode)                                   |                                      | Photolithography     |           |

Table Legend: Si—Silicon; PI—Polyimide; PZT—Lead Zirconate Titanate; Au—Gold; PDMS—Polydimethylsiloxane; Cr—Chromium; Pt—Platinum; Ti—Titanium; Cu—Copper; SiO$_2$—Silicon oxide; GaAr—Gallium argonide; PVA—Poly(vinyl alcohol); Mg—Magnesium; MgO—Magnesium oxide; Ag—Silver; AgCl—Silver chloride.
4. Conclusions and Future Directions

Biosensors are devices capable of detecting target analytes in a sample mixture. They are composed of bioreceptors, and transducers, responsible for the production of a specific signal, that will after be processed in a readable output signal. Biosensors can be applied to a variety of fields, however, monitoring health conditions is their most attractive application. They can be used for early diagnosis and continuous monitoring of high mortality diseases, such as cancer and cardiovascular diseases, significantly contributing to a reduction on mortality rate and the improvement of the patient’s life quality.

Skin-integrated and implantable biosensors envision the analyte detection in human fluids and in loco, which in one hand can provide a more reliable and real time monitoring of the health condition, and in the other hand it adds complexity and technical challenges to the biosensing system. Skin-integrated biosensors can be mounted directly on skin or by using a flexible polymer that will mechanically match skin. Several micro-fabrication techniques and nanomaterials have been used to produce multiple skin-integrated wearable devices, such as bio-potential sensors, sweat sensors and tattoo sensors.

Implantable biosensors need to consider the FBR, which implies the choice of biocompatible materials and fabrication methods. Therefore, biocompatibility and lifetime are the major limitations besides the power methodologies. Approaches for harvesting energy from the body environment have been investigated as an alternative to the conventional battery-based systems for powering the wearable and implantable biosensors. Although, challenges like low output power and restricted implant location choices need to be overcome. On the other hand, power approaches related to inductive coupling or the ultrasonic transducer may allow transferring the power and information data in addition, to the ability to power the devices in different body locations. Nevertheless, there is still room for improvement and optimization in the field of wireless communications and wireless powering.

Significant advances have been made in the field of skin-integrated and wearable biosensors, however, the complexity and multidisciplinary nature of the field leave many technical challenges still to solve. Therefore, finding new ways to avoid FBR, produce sustainable power supplies and data communication are areas where more research needs to be performed, in order for these devices to achieve real world applications.

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**References**

1. Clark, L.C.; Lyons, C. Electrode Systems for Continuous Monitoring in Cardiovascular Surgery. *Ann. N. Y. Acad. Sci.* 1962, 102, 29–45. [CrossRef] [PubMed]
2. Perumal, V.; Hashim, U. Advances in biosensors: Principle, architecture and applications. *J. Appl. Biomed.* 2014, 12, 1–15. [CrossRef]
3. Palchetti, I. Afinity biosensors for tumor-marker analysis. *Bioanalysis* 2014, 6, 3417–3435. [CrossRef] [PubMed]
4. Kumar, S.; Ahlawat, W.; Kumar, R.; Dilbaghi, N. Graphene, carbon nanotubes, zinc oxide and gold as elite nanomaterials for fabrication of biosensors for healthcare. *Biosens. Bioelectron.* 2015, 70, 498–503. [CrossRef]
5. Lee, J. Human Implantable Arrhythmia Monitoring Sensor with Wireless Power and Data Transmission Technique. *Austin J. Biosens. Bioelectron.* 2015, 1, 1008.
6. Rebelo, R.; Barbosa, A.L.; Caballero, D.; Kwon, I.K.; Oliveira, J.M.; Kundu, S.C.; Reis, R.L.; Correlo, V.M. 3D biosensors in advanced medical diagnostics of high mortality diseases. *Biosens. Bioelectron.* 2019, 130, 20–39. [CrossRef]
7. Tanimu, A. Electrochemical Sensors Using Nanomaterials—A Mini Review. *Res. Rev. J. Chem.* 2017, 6, 38–48.
8. Chen, C.; Wang, J. Optical biosensors: An exhaustive and comprehensive review. *Analyst* 2020, 145, 1605–1628. [CrossRef]
36. Lipomi, D.J.; Vosgueritchian, M.; Tee, B.C.K.; Hellstrom, S.L.; Lee, J.A.; Fox, C.H.; Bao, Z. Skin-like pressure and strain sensors based on transparent elastic films of carbon nanotubes. Nat. Nanotechnol. 2011, 6, 788–792. [CrossRef]

37. So, H.M.; Sim, J.W.; Kwon, J.; Yun, J.; Baik, S.; Chang, W.S. Carbon nanotube based pressure sensor for flexible electronics. Mater. Res. Bull. 2013, 48, 5036–5039. [CrossRef]

38. Xuan, X.; Yoon, H.S.; Park, J.Y. A Wearable Electrochemical Glucose Sensor based on Simple and Low-Cost Fabrication Supported Micro-Patterned Reduced Graphene Oxide Nanocomposite Electrode on Flexible Substrate. Biosens. Bioelectron. 2018, 109, 75–82. [CrossRef]

39. Khodagholy, D.; Curto, V.F.; Fraser, K.J.; Gurfinkel, M.; Byrne, R.; Diamond, D.; Malliaras, G.G.; Benito-Lopez, F.; Owens, R.M. Organic electrochemical transistor incorporating an ionogel as a solid state electrolyte for lactate sensing. J. Mater. Chem. 2012, 22, 4440–4443. [CrossRef]

40. Koh, A.; Kang, D.; Xue, Y.; Lee, S.; Pielak, R.M.; Kim, J.; Hwang, T.; Min, S.; Banks, A.; Bastien, P.; et al. A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. Sci. Transl. Med. 2016, 165, 1–14. [CrossRef] [PubMed]

41. Augarten, A.; Hacham, S.; Kerem, E.; Kerem, B.S.; Szeinberg, A.; Laufer, J.; Doolman, R.; Altschuler, R.; Blau, H.; Bentur, L.; et al. The significance of sweat Cl/Na ratio in patients with borderline sweat test. Pediatr. Pulmonol. 1995, 20, 369–371. [CrossRef]

42. Sonner, Z.; Wilder, E.; Gaillard, T.; Kasting, G.; Heikenfeld, J. Integrated sudomotor axon reflex sweat stimulation for continuous sweat analyte analysis with individuals at rest. Lab Chip 2017, 17, 2550–2560. [CrossRef] [PubMed]

43. Choi, J.; Ghaffari, R.; Baker, L.B.; Rogers, J.A. Skin-interfaced systems for sweat collection and analytics. Sci. Adv. 2018, 4, eaar3921. [CrossRef] [PubMed]

44. Kang, J.W.; Park, Y.S.; Chang, H.; Lee, W.; Singh, S.P.; Choi, W.; Galindo, L.H.; Dasari, R.R.; Nam, S.H.; Park, J.; et al. Direct observation of glucose fingerprint using in vivo Raman spectroscopy. Sci. Adv. 2020, 6, 2–10. [CrossRef]

45. Son, D.; Lee, J.; Qiao, S.; Ghaffari, R.; Kim, J.; Lee, J.E.; Song, C.; Kim, S.; Lee, D.; Jun, S.W.; et al. Multifunctional wearable devices for diagnosis and therapy of movement disorders. Nat. Nanotechnol. 2014, 9, 397–404. [CrossRef] [PubMed]

46. Wongkaew, N.; Simsek, M.; Griesche, C.; Baemann, A.J. Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective. Chem. Rev. 2019, 119, 120–194. [CrossRef]

47. Barbosa, A.I.; Borges, J.; Meira, D.I.; Costa, D.; Rodrigues, M.S.; Rebelo, R.; Correlo, V.M.; Vaz, F.; Reis, R.L. Development of label-free plasmonic Au-TiO2 thin film immunosensor devices. Mater. Sci. Eng. C 2019, 100, 424–432. [CrossRef]

48. Wang, Y.; Wang, L.; Yang, T.; Li, X.; Zang, X.; Zhu, M.; Wang, K.; Wu, D.; Zhu, H. Wearable and highly sensitive graphene strain sensors for human motion monitoring. Adv. Funct. Mater. 2014, 24, 4666–4670. [CrossRef]

49. Miyamoto, A.; Lee, S.; Cooray, N.F.; Lee, S.; Mori, M.; Matsuhsia, N.; Jin, H.; Yoda, L.; Yokota, T.; Itoh, A.; et al. Inflammation-free, gas-permeable, lightweight, stretchable on-skin electronics with nanomeshes. Nat. Nanotechnol. 2017, 12, 907–913. [CrossRef]

50. Bandodkar, A.J.; Wang, J. Non-invasive wearable electrochemical sensors: A review. Trends Biotechnol. 2014, 32, 363–371. [CrossRef]

51. Windmiller, J.R.; Bandodkar, A.J.; Parkhomovsky, S.; Wang, J. Stamp transfer electrodes for electrochemical sensing on non-planar and oversized surfaces. Analyst 2012, 137, 1570–1575. [CrossRef]

52. Jia, W.; Bandodkar, A.J.; Valdés-Ramírez, G.; Windmiller, J.R.; Yang, Z.; Ramírez, J.; Chan, G.; Wang, J. Electrochemical tattoo biosensors for real-time noninvasive lactate monitoring in human perspiration. Anal. Chem. 2013, 85, 6553–6560. [CrossRef] [PubMed]

53. Bandodkar, A.J.; Jia, W.; Yardimci, C.; Wang, X.; Ramírez, J.; Wang, J. Tattoo-based noninvasive glucose monitoring: A proof-of-concept study. Anal. Chem. 2015, 87, 394–398. [CrossRef]

54. Bandodkar, A.J.; Hung, V.W.S.; Jia, W.; Valdés-Ramírez, G.; Windmiller, J.R.; Martinez, A.G.; Ramírez, J.; Chan, G.; Kerman, K.; Wang, J. Tattoo-based potentiometric ion-selective sensors for epidermal pH monitoring. Analyst 2013, 138, 123–128. [CrossRef]
55. Qin, Y.; Howlader, M.M.R.; Deen, M.J.; Haddad, Y.M.; Selvaganapathy, P.R. Polymer integration for packaging of implantable biosensors. *Sens. Actuators B Chem.* 2014, 202, 758–778. [CrossRef] [PubMed]

56. Clausen, I.; Glott, T. Development of Clinically Relevant Implantable Pressure Sensors: Perspectives and Challenges. *Sensors* 2014, 14, 17686–17702. [CrossRef] [PubMed]

57. Cavallini, A.; Baj-Rossi, C.; Ghoreishizadeh, S.; De Micheli, G.; Carrara, S. Design, fabrication, and test of a sensor array for perspective biosensing in chronic pathologies. In Proceedings of the 2012 IEEE Biomedical Circuits and Systems Conference (BioCAS), Hsinchu, Taiwan, 28–30 November 2012; pp. 124–127.

58. Hwang, S.W.; Tao, H.; Kim, D.H.; Cheng, H.; Song, J.K.; Rill, E.; Brenckle, M.A.; Panilaitis, B.; Won, S.M.; Kim, Y.S.; et al. A physically transient form of silicon electronics. *Science* 2012, 337, 1640–1644. [CrossRef] [PubMed]

59. Blau, A.; Murr, A.; Wolff, S.; Sernagor, E.; Medini, P.; Iurilli, G.; Ziegler, C.; Benfenati, F. Flexible, all-polymer microelectrode arrays for the capture of cardiac and neuronal signals. *Biomaterials* 2011, 32, 1778–1876. [CrossRef]

60. Vaddiraju, S.; Tomazos, I.; Burgess, D.J.; Jain, F.C.; Papadimitrakopoulos, F. Emerging Synergy between Nanotechnology and Implantable Biosensors: A Review. *Bioinspir. Biomim.* 2010, 5, 1553–1565. [CrossRef]

61. Bazaka, K.; Jacob, M. Implantable Devices: Issues and Challenges. *Electronics* 2012, 2, 1–34. [CrossRef]

62. Kochkodan, V.; Hilal, N. A comprehensive review on surface modified polymer membranes for biofouling mitigation. *Desalination* 2015, 356, 187–207. [CrossRef]

63. Jeerapan, I.; Poorahong, S. Review—Flexible and Stretchable Electrochemical Sensing Systems: Materials, Energy Sources, and Integrations. *J. Electrochem. Soc.* 2020, 167, 037573. [CrossRef]

64. Lee, S.H.; Jeong, C.K.; Hwang, G.T.; Lee, K.J. Self-powered flexible inorganic electronic system. *Nano Energy* 2015, 14, 111–125. [CrossRef]

65. Kim, D.H.; Ghaffari, R.; Lu, N.; Wang, S.; Lee, S.P.; Keum, H.; D’Angelo, R.; Klinker, L.; Su, Y.; Lu, C.; et al. Electronic sensor and actuator webs for large-area complex geometry cardiac mapping and therapy. *Proc. Natl. Acad. Sci. USA* 2012, 109, 19910–19915. [CrossRef] [PubMed]

66. Joung, Y.H. Development of implantable medical devices: From an engineering perspective. *Int. Neurol. J.* 2013, 17, 98–106. [CrossRef]

67. Kvist, P.H.; Iburg, T.; Aalbaek, B.; Gerstenberg, M.; Schoier, C.; Kaastrup, P.; Buch-Rasmussen, T.; Hasselager, E.; Jensen, H.E. Biocompatibility of an enzyme-based, electrochemical glucose sensor for short-term implantation in the subcutis. *Diabetes Technol.* 2006, 8, 546–559. [CrossRef] [PubMed]

68. Onuki, Y.; Upkar, M.P.; Papadimitrakopoulos, F.; Burgess, D.J. A Review of the Biocompatibility of Implantable Devices: Current Challenges to Overcome Foreign Body Response. *J. Diabetes Sci. Technol.* 2008, 2, 1003–1015. [CrossRef] [PubMed]

69. Wang, Y.; Vaddiraju, S.; Gu, B.; Papadimitrakopoulos, F.; Burgess, D.J. Foreign body reaction to implantable biosensors: Effects of tissue trauma and implant size. *J. Diabetes Sci. Technol.* 2015, 9, 966–977. [CrossRef]

70. Avula, M.N.; Rao, A.N.; McGill, L.D.; Grainger, D.W.; Solzbacher, F. Modulation of the foreign body response to implanted sensor models through device-based delivery of the tyrosine kinase inhibitor, masitinib. *Biomaterials* 2013, 34, 9737–9746. [CrossRef]

71. Morais, J.M.; Papadimitrakopoulos, F.; Burgess, D.J. Biomaterials/tissue interactions: Possible solutions to overcome foreign body response. *AAPS J.* 2010, 12, 188–196. [CrossRef]

72. Fallegger, F.; Schiavone, G.; Lacour, S.P. Conformable Hybrid Systems for Implantable Bioelectronic Interfaces. *Adv. Mater.* 2019, 32, 1903904. [CrossRef]

73. Chen, C.; Guo, Y.; Chen, P.; Peng, H. Recent advances of tissue-interfaced chemical biosensors. *J. Mater. Chem. B* 2020, 8, 3371–3381. [CrossRef] [PubMed]

74. Gray, M.; Meehan, J.; Ward, C.; Langdon, S.P.; Kunkler, I.H.; Murray, A.; Argyle, D. Implantable biosensors and their contribution to the future of precision medicine. *Vet. J.* 2018, 239, 21–29. [CrossRef] [PubMed]

75. Franz, S.; Rammelt, S.; Scharnoweber, D.; Simon, J.C. Immune responses to implants—A review of the implications for the design of immunomodulatory biomaterials. *Biomaterials* 2011, 32, 6692–6709. [CrossRef]

76. Wisniewski, N.; Moussy, F.; Reichert, W.M. Characterization of implantable biosensor membrane biofouling. *Fresenius’ J. Anal. Chem.* 2000, 366, 611–621. [CrossRef] [PubMed]

77. Yim, E.K.F.; Leong, K.W. Significance of synthetic nanostructures in dictating cellular response. *Nanomedicine Nanotechnol. Biol. Med.* 2005, 1, 10–21. [CrossRef]
78. Tipnis, R.; Vaddiraju, S.; Jain, F.; Burgess, D.J.; Papadimitrakopoulos, F. Layer-by-layer assembled semipermeable membrane for amperometric glucose sensors. *J. Diabetes Sci. Technol.* 2007, 1, 193–200. [CrossRef]

79. Vallejo-Heligon, S.G.; Klitzman, B.; Reichert, W.M. Characterization of porous, dexamethasone-releasing polyurethane coatings for glucose sensors. *Acta Biomater.* 2014, 10, 4629–4638. [CrossRef]

80. Xie, X.; Doloff, J.C.; Yesilyurt, V.; Sadraei, A.; Mcgarrigle, J.J.; Omami, M.; Veiseh, O.; Farah, S.; Isa, D.; Ghani, S.; et al. Reduction of measurement noise in a continuous glucose monitor by coating the sensor with a zwitterionic polymer. *Nat. Biomed. Eng.* 2018, 2, 894–906. [CrossRef]

81. Zhao, J.; Shi, Q.; Luan, S.; Song, L.; Yang, H.; Shi, H.; Jin, J.; Li, X.; Yin, J.; Stagnaro, P. Improved biocompatibility and antifouling property of polypropylene non-woven fabric membrane by surface grafting zwitterionic polymer. *J. Membr. Sci.* 2011, 369, 5–12. [CrossRef]

82. Wang, Y.; Papadimitrakopoulos, F.; Burgess, D.J. Polymeric “smart” coatings to prevent foreign body response to implantable biosensors. *J. Control. Release* 2013, 169, 341–347. [CrossRef]

83. Zhu, J.; Marchant, R.E. Design properties of hydrogel tissue-engineering scaffolds Expert. *Expert Rev. Med. Devices* 2011, 8, 607–626. [CrossRef] [PubMed]

84. Geckil, H.; Xu, F.; Zhang, X.; Moon, S.; Demirci, U. Engineering hydrogels as extracellular matrix mimics. *Nanomedicine* 2010, 5, 469–484. [CrossRef] [PubMed]

85. Means, A.K.; Dong, P.; Clubb, F.J.; Friedemann, M.C.; Colvin, L.E.; Shrode, C.A.; Coté, G.L.; Grunlan, M.A. A self-cleaning, mechanically robust membrane for minimizing the foreign body reaction: Towards extending the lifetime of sub-Q glucose biosensors. *J. Mater. Sci. Mater. Med.* 2019, 30, 79. [CrossRef] [PubMed]

86. Heo, Y.J.; Shibata, H.; Okitsu, T.; Kawanishi, T.; Takeuchi, S. Long-term in vivo glucose monitoring using fluorescent hydrogel fibers. *Proc. Natl. Acad. Sci. USA* 2011, 108, 13399–13403. [CrossRef]

87. Yoon, H.; Xuan, X.; Jeong, S.; Park, J.Y. Wearable, robust, non-enzymatic continuous glucose monitoring system and its in vivo investigation. *Biosens. Bioelectron.* 2018, 117, 267–275. [CrossRef] [PubMed]

88. Wang, L.; Xie, S.; Wang, Z.; Liu, F.; Yang, Y.; Tang, C.; Wu, X.; Liu, P.; Li, Y.; Saiyin, H.; et al. Functionalized helical fibre bundles of carbon nanotubes as electrochemical sensors for long-term in vivo monitoring of multiple disease biomarkers. *Nat. Biomed. Eng.* 2020, 4, 159–171. [CrossRef] [PubMed]

89. Bai, W.; Yang, H.; Ma, Y.; Chen, H.; Shin, J.; Liu, Y.; Yang, Q.; Kandela, I.; Liu, Z.; Kang, S.; et al. Flexible Transient Optical Waveguides and Surface-Wave Biosensors Constructed from Monocrystalline Silicon. *Adv. Mater.* 2018, 30, 1801584. [CrossRef]

90. Jayant, R.D.; McShane, M.J.; Srivastava, R. In vitro and in vivo evaluation of anti-inflammatory agents using nanoeengineered alginate carriers: Towards localized implant inflammation suppression. *Int. J. Pharm.* 2011, 403, 268–275. [CrossRef] [PubMed]

91. Kastellorizios, M.; Papadimitrakopoulos, F.; Burgess, D.J. Multiple tissue response modifiers to promote angiogenesis and prevent the foreign body reaction around subcutaneous implants. *J. Control. Release* 2015, 214, 103–111. [CrossRef]

92. Vallejo-Heligon, S.G.; Brown, N.L.; Reichert, W.M.; Klitzman, B. Porous, Dexamethasone-loaded polyurethane coatings extend performance window of implantable glucose sensors in vivo. *Acta Biomater.* 2016, 30, 106–115. [CrossRef]

93. Dong, K.; Jia, B.; Yu, C.; Dong, W.; Du, F.; Liu, H. Microbial fuel cell as power supply for implantable medical devices: A novel configuration design for simulating colonic environment. *Biosens. Bioelectron.* 2013, 41, 916–919. [CrossRef]

94. Cadei, A.; Dionisi, A.; Sardini, E.; Serpelloni, M. Kinetic and thermal energy harvesters for implantable medical devices and biomedical autonomous sensors. *Meas. Sci. Technol.* 2014, 25, 012003. [CrossRef]

95. Baj-Rossi, C.; Kilinc, E.G.; Ghoreishizadeh, S.S.; Casarino, D.; Jost, T.R.; Dehollain, C.; Grassi, F.; Pastorino, L.; De Micheli, G.; Carrara, S. Full fabrication and packaging of an implantable multi-panel device for monitoring of metabolites in small animals. *IEEE Trans. Biomed. Circuits Syst.* 2014, 8, 636–647. [CrossRef]

96. Silay, K.M.; Dehollain, C.; Declercq, M. A closed-loop remote powering link for wireless cortical implants. *IEEE Sens. J.* 2013, 13, 3226–3235. [CrossRef]

97. Hwang, G.T.; Byun, M.; Jeong, C.K.; Lee, K.J. Flexible piezoelectric Thin-Film energy harvesters and nanosensors for biomedical applications. *Adv. Healthc. Mater.* 2015, 4, 646–658. [CrossRef]
98. Liu, H.; Zhao, T.; Jiang, W.; Jia, R.; Niu, D.; Qiu, G.; Fan, L.; Li, X.; Liu, W.P.; Chen, B.; et al. Flexible Battery-Less Bioelectronic Implants: Wireless Powering and Manipulation by Near-Infrared Light. *Adv. Funct. Mater.* 2015, 25, 7071–7079. [CrossRef]

99. Park, Y.G.; Lee, S.; Park, J.U. Recent progress in wireless sensors for wearable electronics. *Sensors* 2019, 19, 1–34. [CrossRef]

100. Chaki, J.; Dey, N.; De, D. *Smart Biosensors in Medical Care*; Chaki, J., Dey, N., De, D., Eds.; Elsevier: Amsterdam, The Netherlands, 2020.

101. Ponnusamy, V.; ZamanNoor, N.; Low, T.J.; Amin, A.H.M. Biologically-Inspired Energy Harvesting through Wireless Sensor Technologies; Ponnusamy, V., Zaman, N., Low, T.J., Amin, A.H.M., Eds.; Advances in Environmental Engineering and Green Technologies; IGI Global: Hershey, PA, USA, 2016; ISBN 9781466697928.

102. Hanks, E.K. *Nano-Safety: What We Need to Know to Protect Workers*; Hanks, C., Fazarro, D.E., Trybula, W., Tate, J., Eds.; De Gueter: Berlin, Germany, 2017.

103. Jiang, H.; Zhang, J.; Lan, D.; Chao, K.K.; Liou, S.; Shahnasser, H.; Fechter, R.; Hirose, S.; Harrison, M.; Roy, S. A low-frequency versatile wireless power transfer technology for biomedical implants. *IEEE Trans. Biomed. Circuits Syst.* 2013, 7, 526–535. [CrossRef]

104. Ho, J.S.; Yeh, A.J.; Neofytou, E.; Kim, S.; Tanabe, Y.; Patlolla, B.; Beygui, R.E.; Poon, A.S.Y. Wireless power transfer to deep-tissue microimplants. *Proc. Natl. Acad. Sci. USA* 2014, 111, 7974–7979. [CrossRef]

105. Bakula, M.; Pelgrims, P.; Puers, R. A wireless powering and communication system for implantable devices based on a Royer oscillator with radio and near-field communication links. *Procedia Eng.* 2015, 120, 306–309. [CrossRef]

106. He, Q.; Liu, J.; Yang, B.; Wang, X.; Chen, X.; Yang, C. MEMS-based ultrasonic transducer as the receiver for wireless power supply of the implantable microdevices. *Sens. Actuators A Phys.* 2014, 219, 65–72. [CrossRef]

107. Shon, A.; Chu, J.U.; Jung, J.; Kim, H.; Youn, I. An implantable wireless neural interface system for simultaneous recording and stimulation of peripheral nerve with a single cuff electrode. *Sensors* 2018, 18, 1.

108. Hanks, E.K. *Nano-Safety: What We Need to Know to Protect Workers*; Hanks, C., Fazarro, D.E., Trybula, W., Tate, J., Eds.; De Gueter: Berlin, Germany, 2017.

109. Liu, H.; Zhao, T.; Jiang, W.; Jia, R.; Niu, D.; Qiu, G.; Fan, L.; Li, X.; Liu, W.P.; Chen, B.; et al. Flexible Battery-Less Bioelectronic Implants: Wireless Powering and Manipulation by Near-Infrared Light. *Adv. Funct. Mater.* 2015, 25, 7071–7079. [CrossRef]

110. Park, K.I.; Son, J.H.; Hwang, G.T.; Jeong, C.K.; Ryu, J.; Koo, M.; Choi, I.; Lee, S.H.; Byun, M.; Wang, Z.L.; et al. Highly-efficient, flexible piezoelectric PZT thin film nanogenerator on plastic substrates. *Adv. Mater.* 2014, 26, 2514–2520. [CrossRef]

111. Shin, S.H.; Kim, Y.H.; Lee, M.H.; Jung, J.Y.; Nah, J. Hemispherically aggregated BaTiO3 nanoparticle composite thin film for high-performance flexible piezoelectric nanogenerator. *ACS Nano* 2014, 8, 2766–2773. [CrossRef]

112. Karker, N.; Dharmalingam, G.; Carpenter, M.A. Thermal energy harvesting plasmonic based chemical sensors. *ACS Nano* 2014, 8, 10953–10962. [CrossRef]

113. Katz, E. Implantable biofuel cells operating in vivo: Providing sustainable power for bioelectronic devices: From biofuel cells to cyborgs. In Proceedings of the 2015 6th International Workshop on Advances in Sensors and Interfaces (IWASI), Gallipoli, Italy, 18–19 June 2015.

114. Ghosh, S.K.; Mandal, D. Sustainable Energy Generation from Piezoelectric Biomaterial for Noninvasive Physiological Signal Monitoring. *ACS Sustain. Chem. Eng.* 2017, 5, 8836–8843. [CrossRef]

115. du Toit, H.; Di Lorenzo, M. Continuous power generation from glucose with two different miniature flow-through enzymatic biofuel cells. *Biosens. Bioelectron.* 2015, 69, 199–205. [CrossRef]

116. Zebda, A.; Cosnier, S.; Alcaraz, J.P.; Holzinger, M.; Le Goff, A.; Gondran, C.; Boucher, F.; Giroud, F.; Gorgy, K.; Lamraoui, H.; et al. Single glucose biofuel cells implanted in rats power electronic devices. *Sci. Rep.* 2013, 3, 1–5. [CrossRef]

117. Wu, T.; Redouté, J.M.; Yuce, M.R. A Wireless Implantable Sensor Design with Subcutaneous Energy Harvesting for Long-Term IoT Healthcare Applications. *IEEE Access* 2018, 6, 35801–35808. [CrossRef]

118. Bertini, M.; Marcantoni, L.; Toselli, T.; Ferrari, R. Remote monitoring of implantable devices: Should we continue to ignore it? *Int. J. Cardiol.* 2016, 202, 368–377. [CrossRef] [PubMed]

119. Cheung, C.C.; Deyell, M.W. Remote Monitoring of Cardiac Implantable Electronic Devices. *Can. J. Cardiol.* 2018, 34, 941–944. [CrossRef] [PubMed]
120. Ferguson, J.E.; Redish, A.D. Wireless communication with implanted medical devices using the conductive properties of the body. Expert Rev. Med. Devices 2011, 8, 427–433. [CrossRef]

121. Dakurah, M.N.; Koo, C.; Choi, W.; Joung, Y.H. Implantable bladder sensors: A methodological review. Int. Neurourol. J. 2015, 19, 133–141. [CrossRef] [PubMed]

122. Tsujimura, S.; Yamagishi, H.; Sankai, Y. Development of a bidirectional data communication system using ultra high frequency radio wave for implantable artificial hearts. In Proceedings of the TENCON 2010–2010 IEEE Region 10 Conference, Fukuoka, Japan, 21–24 November 2010.

123. Asgari, S.S.; Bonde, P. Implantable physiologic controller for left ventricular assist devices with telemetry capability. J. Thorac. Cardiovasc. Surg. 2014, 147, 192–202. [CrossRef]

124. Kilinc, E.G.; Baj-Rossi, C.; Ghoreishizadeh, S.; Riario, S.; Stradolini, F.; Boero, C.; De Micheli, G.; Maloberti, F.; Carrara, S.; Gehollain, C. A System for Wireless Power Transfer and Data Communication of Long-Term Bio-Monitoring. IEEE Sens. J. 2015, 15, 6559–6569. [CrossRef]

125. Ryou, M.; Nemiroski, A.; Azagury, D.; Shaikh, S.N.; Ryan, M.B.; Westervelt, R.M.; Thompson, C.C. An implantable wireless biosensor for the immediate detection of upper GI bleeding: A new fluorescein-based tool for diagnosis and surveillance (with video). Gastrointest. Endosc. 2011, 74, 189–194. [CrossRef]

126. Aldaoud, A.; Laurenson, C.; Rivet, F.; Yuce, M.R.; Redoute, J.M. Design of a miniaturized wireless blood pressure sensing interface using capacitive coupling. IEEE/ASME Trans. Mechatron. 2015, 20, 487–491. [CrossRef]

127. Olivo, J.; Carrara, S.; De Micheli, G. Micro-fabrication of high-thickness spiral inductors for the remote powering of implantable biosensors. Microelectron. Eng. 2014, 113, 130–135. [CrossRef]

128. Luo, M.; Martinez, A.W.; Song, C.; Herrault, F.; Allen, M.G. A microfabricated wireless RF pressure sensor made completely of biodegradable materials. J. Micromechanics Microeng. 2014, 23, 4–13. [CrossRef]

129. Lee, J.H. Miniaturized Human Insertable Cardiac Monitoring System with Wireless Power Transmission Technique. J. Sens. 2016, 2016, 5374574. [CrossRef]

130. Lee, J.-H.; Seo, D.-W. Development of ECG Monitoring System and Implantable Device with Wireless Charging. Micromachines 2019, 10, 38. [CrossRef]

131. Mulberry, G.; White, K.A.; Kim, B.N. A Wirelessly Powered Implantable CMOS Neural Recording Sensor Array using Pulse-based Neural Amplifier. bioRxiv 2019, 809509.

132. Vennemann, B.; Obrist, D.; Rösgen, T. A smartphone-enabled wireless and batteryless implantable blood flow sensor for remote monitoring of prosthetic heart valve function. PLoS ONE 2020, 15, e0227372. [CrossRef]

133. Pang, C.; Lee, C.; Suh, K.Y. Recent advances in flexible sensors for wearable and implantable devices. J. Appl. Polym. Sci. 2013, 130, 1429–1441. [CrossRef]

134. Yang, G.-Z. Implantable Sensors and Systems: From Theory to Practice; Yang, G.-Z., Ed.; Springer: Berlin/Heidelberg, Germany, 2018.

135. Thedor, M.; Fiala, J.; Ruh, D.; Förster, K.; Heilmann, C.; Beyersdorf, F.; Manoli, Y.; Zappe, H.; Seifert, A. Implantable accelerometer system for the determination of blood pressure using reflected wave transit time. Sens. Actuators A Phys. 2014, 206, 151–158. [CrossRef]

136. Viventi, J.; Kim, D.H.; Moss, J.D.; Kim, Y.S.; Blanco, J.A.; Annetta, N.; Hicks, A.; Xiao, J.; Huang, Y.; Callans, D.J.; et al. A conformal, bio-interfaced class of silicon electronics for mapping cardiac electrophysiology. Sci. Transl. Med. 2010, 2, 1–5. [CrossRef]

137. Khan, S.; Lorenzelli, L.; Dahiya, R.S. Technologies for printing sensors and electronics over large flexible substrates: A review. IEEE Sens. J. 2015, 15, 3164–3185. [CrossRef]

138. Viventi, J.; Kim, D.; Vigeland, L.; Frechette, E.S.; Blanco, J.A.; Kim, Y.; Avrin, A.E.; Tiruvadi, V.R.; Hwang, S.; Vanleer, A.C.; et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. Nat. Neurosci. 2011, 14, 1599–1605. [CrossRef]

139. Kim, D.H.; Viventi, J.; Amsden, J.J.; Xiao, J.; Vigeland, L.; Kim, Y.S.; Blanco, J.A.; Panilaitis, B.; Frechette, E.S.; Contreras, D.; et al. Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics. Nat. Mater. 2010, 9, 511–517. [CrossRef]

140. Lu, B.; Chen, Y.; Ou, D.; Chen, H.; Diao, L.; Zhang, W.; Zheng, J.; Ma, W.; Sun, L.; Feng, X. Ultra-flexible Piezoelectric Devices Integrated with Heart to Harvest the Biomechanical Energy. Sci. Rep. 2015, 5, 16065. [CrossRef] [PubMed]
141. Kim, D.H.; Lu, N.; Ghaffari, R.; Kim, Y.S.; Lee, S.P.; Xu, L.; Wu, J.; Kim, R.H.; Song, J.; Liu, Z.; et al. Materials for multifunctional balloon catheters with capabilities in cardiac electrophysiological mapping and ablation therapy. *Nat. Mater.* 2011, 10, 316–323. [CrossRef] [PubMed]

142. Park, D.W.; Schendel, A.A.; Mikael, S.; Brodnick, S.K.; Richner, T.J.; Ness, J.P.; Hayat, M.R.; Atry, F.; Frye, S.T.; Pashaie, R.; et al. Graphene-based carbon-layered electrode array technology for neural imaging and optogenetic applications. *Nat. Commun.* 2014, 5, 1–11. [CrossRef]

143. Minev, I.R.; Musienko, P.; Hirsch, A.; Barraud, Q.; Wenger, N.; Moraud, E.M.; Gandar, J.; Capogrosso, M.; Milekovic, T.; Asboth, L.; et al. Electronic dura mater for long-term multimodal neural interfaces. *Science* 2015, 347, 159–163. [CrossRef]

144. Wen, X.; Wang, B.; Huang, S.; Lee, M.S.; Chung, P.S.; Chow, Y.T.; Huang, I.W.; Monbouquette, H.G.; Maidment, N.T.; Chiou, P.Y. Flexible, multifunctional neural probe with liquid metal enabled, ultra-large tunable stiffness for deep-brain chemical sensing and agent delivery. *Biosens. Bioelectron.* 2019, 131, 37–45. [CrossRef]

145. Liu, L.; Zhao, F.; Liu, W.; Zhu, T.; Zhang, J.Z.H.; Chen, C.; Dai, Z.; Peng, H.; Huang, J.L.; Hu, Q.; et al. An Electrochemical Biosensor with Dual Signal Outputs: Toward Simultaneous Quantification of pH and O2 in the Brain upon Ischemia and in a Tumor during Cancer Starvation Therapy. *Angew. Chem. Int. Ed.* 2017, 56, 10471–10475. [CrossRef]

146. Liu, X.; Xiao, T.; Wu, F.; Shen, M.Y.; Zhang, M.; Yu, H.H.; Mao, L. Ultrathin Cell-Membrane-Mimic Phosphorylcholine Polymer Film Coating Enables Large Improvements for In Vivo Electrochemical Detection. *Angew. Chem. Int. Ed.* 2017, 56, 11802–11806. [CrossRef]

147. Hébert, C.; Scorsone, E.; Bendali, A.; Kiran, R.; Cottance, M.; Girard, H.A.; Degardin, J.; Dubus, E.; Lissorgues, G.; Rousseau, L.; et al. Boron doped diamond biotechnology: From sensors to neurointerfaces. *Faraday Discuss.* 2014, 172, 47–59. [CrossRef]

148. Weng, X.; Ahmed, S.R.; Neethirajan, S. A nanocomposite-based biosensor for bovine haptoglobin on a 3D paper-based analytical device. *Sens. Actuators B Chem.* 2018, 265, 242–248. [CrossRef]

149. Lee, Y.J.; Park, S.J.; Yun, K.S.; Kang, J.Y.; Lee, S.H. Enzymeless glucose sensor integrated with chronically implantable nerve cuff electrode for in-situ inflammation monitoring. *Sens. Actuators B Chem.* 2016, 222, 425–432. [CrossRef]

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