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Review

Material Design in Implantable Biosensors toward Future Personalized Diagnostics and Treatments

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Abstract: The growing demand for personalized treatments and the constant observation of vital signs for extended periods could positively solve the problematic concerns associated with the necessity for patient control and hospitalization. The impressive development in biosensing devices has led to the creation of man-made implantable devices that are temporarily or permanently introduced into the human body, and thus, diminishing the pain and discomfort of the person. Despite all promising achievements in this field, there are some critical challenges to preserve reliable functionality in the complex environment of the human body over time. Biosensors in the in vivo environment are required to have specific features, including biocompatibility (minimal immune response or biofouling), biodegradability, reliability, high accuracy, and miniaturization (flexible, stretchable, lightweight, and ultra-thin). However, the performance of implantable biosensors is limited by body responses and insufficient power supplies (due to minimized batteries/electronics and data transmission without wires). In addition, the current processes and developments in the implantable biosensors field will open new routes in biomedicine and diagnostic systems that monitor occurrences happening inside the body in a certain period. This topical paper aims to give an overview of the state-of-the-art implantable biosensors and their design methods. It also discusses the latest developments in material science, including nanomaterials, hydrogel, hydrophilic, biomimetic, and other polymeric materials to overcome failures in implantable biosensors' reliability. Lastly, we discuss the main challenges faced and future research prospects toward the development of dependable implantable biosensors.

Keywords: implantable biosensors; diagnostics; therapy; polymers; nanomaterials; composites

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1. Introduction

One of the biggest concerns of human beings in all eras has been the diagnosis and treatment of different disorders and ultimately advancing quality of life. The remarkable progress in various scientific fields (physics, electronics, mechanics, chemistry, biochemistry, computer, and medicine) has led to the creation of new diagnostic and therapeutic methods and devices by employing the already-existing techniques and tools at hand. Biosensors have been one of the most successful outputs of supplementary science, especially after the first invention of a glucose biosensor in 1962 [1]. They found their proper place in various fields, including biomedicine, bioprocessing, homeland security, food safety, agriculture, environmental, and industrial monitoring. What is known today as pervasive computing (people interaction environment with various companions, embedded, and invisible computers) could bring the application and performance of biosensors to a higher level. Pervasive computing technology provides the automatic environmental reaction to the user's computing needs without spending time and energy. The implantation of

micro-sensors in the human body is an essential part of pervasive computing. This technology's application undeniably provides high-performance, proportionally inexpensive, and people-centered solutions for health care and monitoring. Such a system, centralizing each patient individually, reduces the burden on society's health systems, expended time and costs, and the risk of incorrect diagnosis and treatment while requiring low sample volumes and fewer testing reagents.

2. Implantable Biosensors and Their Design

Implantable devices were introduced in the early 20th century and with technological developments, the concept of implantable biosensors has seen many breakthroughs (Figure 1). Implantable biosensors consist of (i) a wireless sensing network inside the human body and (ii) some external entities outside of the body that are responsible for data collection and dissemination, respectively [2,3]. For instance, implantable biosensors in the subcutaneous skin layer, nasal area, and tongue can recognize toxins in ingested food and inhaled air. Depending on the biosensor infrastructures, these devices can take corrective action after toxin detection or inform the host about it. The retina implantable biosensors are another success, where the biosensor collects light signals from outside and stimulates the optical cells to give partial vision [4]. Since the invention of implantable biosensors, many of them have been approved by the FDA and reached industrialization, such as cochlear, heart pacemakers, and vagus nerve stimulators [5–8]. Despite all the positive impacts of implantable devices on medical care and treatment, their side effects and high cost are still thought-provoking [9]. Changing materials and manipulating devices' architectures are among the primary strategies selected to reduce or eliminate such consequences [10].

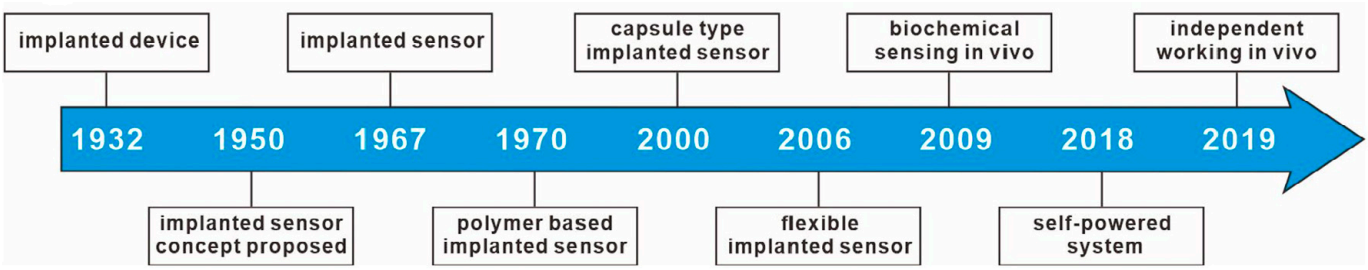

Figure 1. Timeline of implantable sensors developments. Reproduced with permission from ref. [11]. ©2021 Wiley Periodicals LLC.

The materials used in implantable biosensors must have in vivo biocompatibility, mechanical suitability, flexibility, and biodegradability. The in vivo biocompatibility experimentation is hardly recommended due to the different body responses to foreign materials [5–8]. Introducing foreign materials into the human body causes some biological reactions (i.e., host response) that lead to tissue or organ malfunction. Other than biocompatibility, the flexibility of the materials is an important criterion due to the soft nature of tissues and organs and the ability of the device to adhere to its allocated and targeted region [12,13]. Moreover, the morphology and size of the device are important parameters. The chance of biological rejection is high for bulky devices [12]. Although implantable devices with good biocompatibility and soft materials are suitable for clinical application, the long-term presence of foreign substances in the body can increase the risk of malfunction, inflammation, and deformity of tissues. In most cases, a second surgery is needed to externalize the implanted instruments, which has its own concerns and risks. In addition, there are limitations in terms of accuracy and effectiveness in certain clinical applications, such as the treatment of large or metastatic tumors (Table 1). Post-market surveillance and human factor studies are important tools in ensuring the safety and effectiveness of implanted devices, but they also face challenges such as limited resources and funding, difficulties in identifying and reporting adverse incidents, and potential for bias in reporting and data collection. Overall, while implantable sensors have great potential

for improving healthcare outcomes, their development and use must be approached with caution and careful consideration of the risks and benefits [14,15].

Table 1. Advantages and disadvantages of clinical applications of implantable biosensors and evaluation of their post market surveillance and human factor studies [14,15].

Clinical Application	Advantages	Disadvantages
Brain stimulator	- Can help manage neurological disorders such as epilepsy and Parkinson's disease. - Provides continuous monitoring and stimulation. - Small and lightweight	- Requires invasive surgery for implantation. - Risk of infection or damage to surrounding tissue. - Potential for device malfunction or failure.
Heart failure monitoring	- Allows for continuous monitoring of heart function. - Can provide early warning of heart failure and prevent hospitalization. - Enables personalized treatment and management.	- Requires invasive surgery for implantation. - Risk of infection or damage to surrounding tissue. - Potential for device malfunction or failure.
Blood glucose level	- Provides continuous monitoring of glucose levels. - Allows for personalized insulin dosing and management. - Can improve quality of life and reduce complications.	- Requires invasive surgery for implantation. - Risk of infection or damage to surrounding tissue. - Potential for device malfunction or failure. - Accuracy of measurements may be affected by factors such as temperature and medication.
Cancer treatment	- Can provide targeted, localized treatment of tumors. - Reduces side effects of systemic chemotherapy. - Allows for personalized treatment and management.	- Requires invasive surgery for implantation - Risk of infection or damage to surrounding tissue. - Potential for device malfunction or failure. - Limited effectiveness in treating large or metastatic tumors.
Post-market surveillance	- Allows for early detection and management of device-related complications. - Helps ensure safety and effectiveness of implanted devices.	- Limited resources and funding for surveillance and monitoring. - Difficulties in identifying and reporting adverse incidents. - Potential for bias in reporting and data collection.
Human factor studies	- Helps ensure safety and effectiveness of implanted devices. - Provides insights into patient experience and satisfaction. - Enables personalized treatment and management.	- Limited resources and funding for studies. - Difficulties in recruiting participants and obtaining informed consent. - Potential for bias in study design and data collection.

As such, devices composed of biodegradable materials have become favored to overcome these issues [16]. These devices can be degraded through the metabolic processes that happen in the body (complete or partial degradation) [2,17]. Some materials, such as metals (e.g., zinc, molybdenum, and magnesium) have been used as conductors. Other materials such as silicon, zinc oxide, or silicon oxide and nitride (SiNx) are used as nanomembranes, semiconductors, or insulators, respectively. Additionally, polymers containing an ester group (RCOOR'), including polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), or poly(glycerol sebacate) (PGS), were used as substrates because they can be cleaved by

water molecules found in the blood, which results in a byproduct that is both soluble and absorbable by the body [2].

Other than the host response of the human body to implantable biosensors, the chances of devices breaking down and malfunctioning in the body after a long time are high [18]. The most common reason is the repeated motion and size change of organs and tissues. To overcome this lack, self-healable materials with the ability to create energy dissipation mechanism-based reversible chemical bands and adaptable geometry are worthy of being utilized [19,20]. Another criterion to mention in the design of implantable sensors is their power suppliers, which often need to be out-of-body sources, that cause some drawbacks, including implantation complexity, discomfort of subjects, and infection risks [2,21]. The present solutions are designed around using two types of wireless communication tools: (i) passive devices (based on electromagnetic transmitters or readers) and (ii) chip-integrated devices (based on the measurement of electrical signals sent from the chip) [21,22]. However, the choice of devices should be meticulously selected depending on the intended use. The passive component-based devices are more favored due to the flexibility, self-healing ability, biocompatibility, and biodegradability of the applied substances and their lack of need for a hard and voluminous chip nor an inner power source (Figure 2) [2,3]. However, passive sensors have limited temporal resolution and poor performance when measuring multiple or complex parameters, limiting their use as implantable sensors in many medical applications. They also suffer from measurement frequency where they take minutes to acquire data compared to active sensors especially in situations where continuous or several measurements per second are necessary, as in the case of orthopedic monitoring [23].

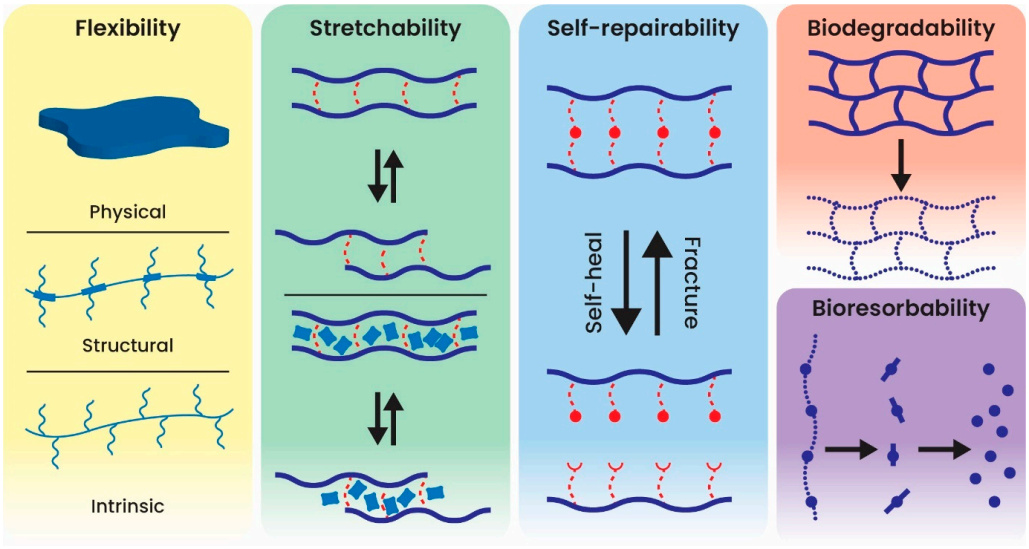

Figure 2. Representation of the properties desired in materials aimed for implantation applications.

Besides the concept of material design and device architecture, the insertion of the device into the body is one of the serious concerns for researchers in this field. There are huge numbers of complaints about conventional insertions by surgeries which cause physical suffering and infections, long recovery times, high cost, and possible psychological problems. To avoid such complaints, minimally-invasive surgery (MIS), such as catheter-based treatment and laparoscopic surgery, with considerably fewer side effects have been introduced as standard medical procedures [24]. The inspiration by the positive feedback of MIS has led to the introduction of an advanced version of the technique called the minimally invasive insertion of implantable devices. This approach consists of syringe-injectable devices that can be inserted into the body by MIS (Figure 3) [25–28]. For instance, Qazi et al. reported inserting mesh-like electric materials constructed with an epoxy-based negative photoresist into a living mouse via an MIS procedure (Figure 3A). The mouse's brain activity was effectively assessed, indicating the potential of this approach

for clinical applications [27]. Another successful study by Whyte et al. described the insertion of a flexible mesh made from shape-memory polymer for tissue delivery [28]. This elastic scaffold was made using a UV-cross-linkable and biodegradable elastomer known as POMaC (poly(octamethylene maleate (anhydride) citrate)) which was able to deliver cardiac tissues to the heart via MIS.

Other than syringe-injectable devices, inflatable balloon catheters are considered the best option in many clinical operations [29,30]. These devices showed some significant features, including MIS-based insertions using tiny incisions, controlled inflation, small size due to the cylindrical form when it is deflated, and optimal application due to the soft contact with surrounding tissues [30]. However, the lack of functionality in these devices limited their practical applications. To overcome this lack, adding functionality to the catheters by integrating electronics was considered [29]. In the developed version, a balloon catheter is used as a base for the incorporation of sensors, heaters, etc. For instance, Whyte et al. proposed tube-based medical treatment as a sustainable therapeutic delivery approach (Figure 3C) [28].

There are some other splendid examples of minimally invasive insertions. For example, Park et al. described the use of a minimally invasive insertion for implanting a one-step fiber-based optogenetics system in a human body (Figure 3D) [31]. This simple and multifunctional approach exhibited the potentiality of optogenetics implementation due to the ease and cost-effectiveness of the approach. Personalization should be considered when designing implantable devices due to the different body sizes and shapes of each organism. Using some new techniques, such as 3D printers, could be significantly influential.

Rigidity is another critical parameter affecting the insertion in challenging mediums such as skin. The materials with high rigidity can cause in vivo inflammation in targeted tissues and organs making the use of rigid devices inconvenient. On the other hand, emerging soft, flexible, and stretchable electronics are more appropriate for use in wearables and implants. This is because they can adjust to the natural deformation of bodily tissue, which greatly enhances comfort, portability, and facilitates continuous monitoring of physiological functions. However, the use of soft electronics in applications outside of the body can pose challenges in handling and interfacing because these devices may not be able to withstand high contact forces and loads [12,32,33]. To deal with such a contradiction, an innovative concept in device implantation strategies using transformable electronics was introduced (Figure 3E). Transformable electronics are composed of melted metals such as gallium with melting points under the average human body temperature. The specific melting temperature of these metals makes the substrate soft inside the body but rigid outside of it [12].

In addition to the nature of the material used and the insertion strategies, another effective factor in the design is the ability of the implantable devices to adhere to the target tissues and organs. The adhesion subject can be seen from two points of view: (i) long-term and (ii) short term implantable devices. Short-term adhesion is achieved through pressure-sensitive adhesives or suction and is suitable for sensors that only need to be in place for a few hours or days. The advantages of short-term adhesion are the easy and painless removal of the sensor after use, without causing damage to the tissue or leaving residue, and lower cost than long-term adhesives. However, it may not hold the sensor in place during movement or physical activity and can cause skin irritation or allergic reactions. Long-term adhesion is achieved through biocompatible materials such as silicone, hydrogels, or other polymers that form strong bonds with the tissue. It is suitable for sensors that need to remain in place for extended periods of time, ranging from days to years. The main advantage of long-term adhesion is that it provides a more reliable and stable attachment, allowing for continuous monitoring without frequent repositioning or replacement. However, removing long-term adhesives can be more difficult and painful, and they can be more expensive than short-term adhesives [34].

The presence of surrounding biological fluids around the surface of tissues or organs creates a moist environment that prevents the addition of any implantable device.

Some invasive methods include using mechanical joints (helixes or corkscrews) to fix the devices [35]. In this case, other than the probability of inflammation, limitations by the severe fibrosis of muscular layers may cause malfunctioning and difficulty removing the device [36]. Hydrogel-based materials could be used as precious replacements with their ultra-softness and plentiful functional groups. Li et al. described the preparation of a hydrogel with enhanced adhesion towards several wet surfaces (i.e., organ surfaces) (Figure 3F) [37]. In their proposed strategy, strong chemical bonds between the hydrogel and the organ surface could keep the device in the targeted site. Unfortunately, the adhesion method used in the mentioned study is diffusion-based, which is time-consuming to create chemical bands. Alternatively, Yuk et al. suggested using a double-sided dry tape that is capable of a quick and strong attachment to different wet surfaces with mild pressure (Figure 3G) [38]. Lee et al. created a patch with ambivalent surface chemistry consisting of a hydrophilic site for attachment to the organ's surface and a hydrophobic side for encapsulating the medicine [3].

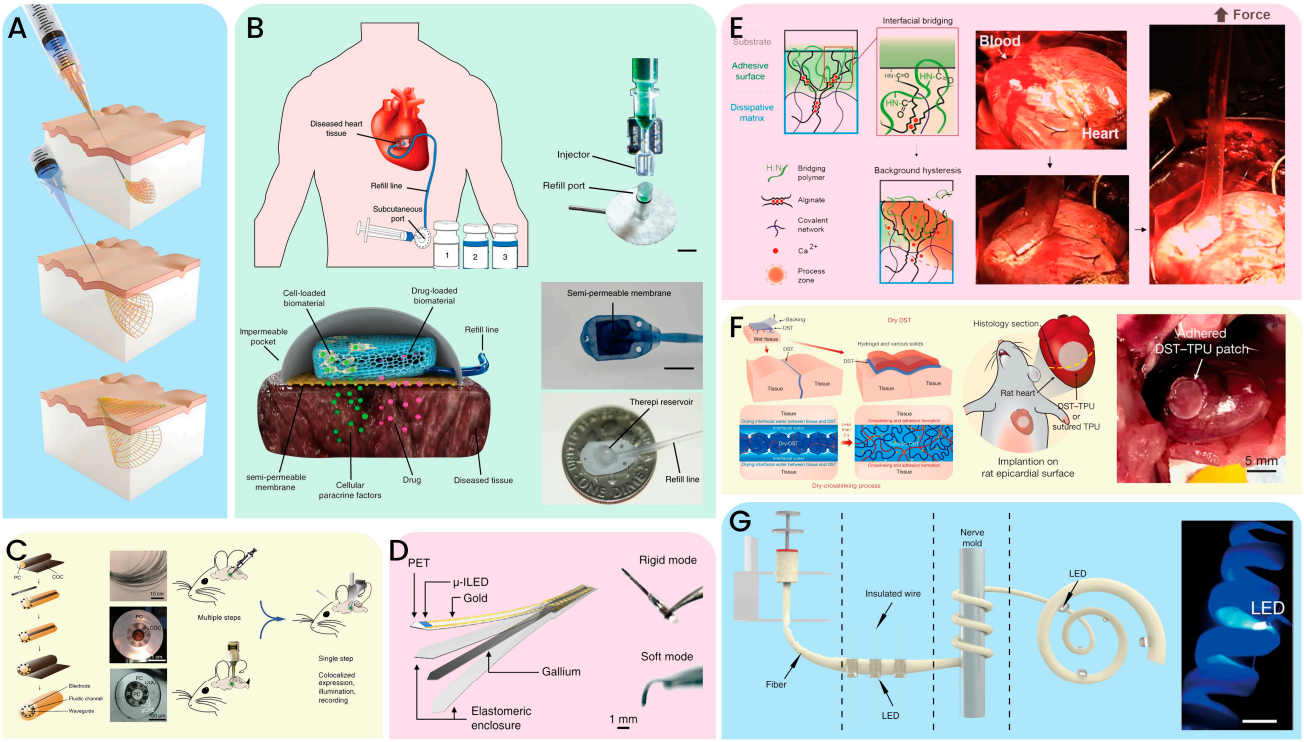

Figure 3. Minimally invasive surgery (MIS) approaches. (**A**) Electronics injected via syringes. Reproduced with permission from ref. [25]. ©2015 Nature. (**B**) Tube-based tissue delivery via MIS. Reproduced with permission from ref. [28]. ©2018 Nature. (**C**) MIS functional fiber for optogenetics. Reproduced with permission from ref. [31]. ©2017 Nature. (**D**) Transformable electronic implantable sensor [12]. (**E**) Tough adhesion formation on a wet surface and hydrogel-based tough adhesive mounting on a heart. Reproduced with permission from ref. [37]. ©2017 AAAS. (**F**) Tough adhesion formation between tissue and dry double-sided tape and its mounting on a heart. Reproduced with permission from ref. [38]. ©2019 Nature. (**G**) Shape memory polymer-based optical neuromodulation device [39].

The attachment and adhesion of implantable devices on nerve tissues is an encouraging approach for treating neurological disorders such as ischemic, pelvic, and Parkinson's disorders. In conventional methods, cylindrical cuff electrodes have been surrounding nerve tissues, creating damage and inflammation due to the rigid and hard structure of the devices. To address this issue, Zheng et al. applied an original structure of a soft optical neuromodulation device able to memorize the spiral form leading to self-wrapping around a targeted nerve tissue without an additional surgical process [39]. The whole procedure

is controlled by optical stimulation without any noticeable side effects. In conclusion, the correct selection of the constructive material, insertion methods, and the ability to attach properly to the targeted tissues and organs without invasive surgical methods can offer a base for next-generation medical treatments strategies based on soft implantable devices.

3. Classification of Implantable Biosensors Based on Material Design

Undoubtedly, the development and application of biosensors, specifically wearable and implantable devices, significantly impacts the quality of life and, consequently, correct investment in biomedical systems. In general, biosensors and, later, implantable biosensors are classified based on the quantity to be measured, including physical, electrical, or chemical. The continuous measurement of such qualities without patients' intrusion and patients' physiological state (walking, rest, exercise, etc.) is an essential criterion for choosing the type of implantable biosensor. As mentioned before, the specific size and morphology of the device, as well as the long operational lifetime, should be precisely considered in material design and format. For instance, the destruction of the protective cover of the implantable sensors due to protein adsorption or cellular deposits and, as a result, releasing free chemicals between the body fluids and sensor, could cause inflammation of tissue, infection, or clotting in a vascular site reaction which results in un-trustable measurements [40]. Therefore, the materials used in implantable biosensors must be biocompatible and biodegradable.

3.1. Electrochemical Active-Based Implantable Biosensors

The two main constructive parts of each biosensor include a bio-recognition element that recognizes a target and a transducer that translates the molecular interaction into an electrical signal. Proteins, peptides, enzymes, antibodies, and nucleic acids are widely employed as detection components in biosensors. In electrochemical devices, electrodes that are transduction elements explore the intrinsic electron transfer nature of recognition elements throughout biochemical reactions. Electrochemical implantable devices are generally assembled on three-electrode or two-electrode systems with the latter having both the reference and counter electrodes combined into one. In such a system, the potential of the working electrode is influenced by a potentiostat to direct electrode reactions with immobilized enzymes for a complete catalytic turnover. The electrochemical biosensors, which can be divided into voltammetric and amperometric biosensors, can evaluate faradaic currents (fixed or varied potentials). They are ion-selective, conductometric, and field-effect transistor-based sensors. Amongst all metals, stainless steel or noble materials such as gold and other different alloys (i.e., platinum-tungsten or iridium oxide) are typically used as fundamental materials for forming strong metal electrodes. Regardless of the type of materials used, electrochemical implantable biosensors, based on their application, can be categorized into implantable glucose biosensors [41], implantable blood-gas, pH, electrolyte, and ion-selective field-effect transistor sensors [42–44].

In electrochemical implantable devices, using high-quality electrodes to diminish motion artifacts and record accurate, stable, and undistorted signals, are unavoidable and necessary. Other than changing the local analyte concentration at the sensing site due to the corrosive nature of the body liquid (provoking thrombus, inflammatory reactions, and capsule formation), they trigger a sequence of effects such as electrode passivation and membrane biodegradation, which limit the choice of materials. To avoid these issues, the most logical and practical solution is material biocompatibility improvement through the application of suitable bulk materials or modification of their derivatives to facilitate the adsorption of proteins and cells [45]. Among the developed biocompatible materials, polymers are coming in first place. Polymeric materials such as poly(ethyleneglycol), polyvinylchloride, polyurethanes, silicon rubber, Nafion, cellulose, chitosan, and phospholipids exhibit good performance in electrochemical implantable devices. It is important to mention that in converting materials to biocompatible compounds, some of the functionalities of the original materials will be lost. This mostly happens for polymeric materials used in potentiometric sensors. Conducting polymers, on the other hand, are another category

of polymers that have been used as sensing elements in implantable biosensors due to their ability to transduce biological signals into electrical signals. Additionally, conducting polymers can be easily modified to improve selectivity and sensitivity, making them an attractive choice for biosensing applications. However, the use of polymers in implantable biosensors also poses some challenges, such as the potential for foreign-body response and the need for biodegradability or bioresorbability in some contexts [46,47].

Other than biocompatibility, permeability and permselectivity are two other important factors for selecting constructive materials in implantable electrochemical sensors. The performance of implantable amperometric sensors is defined by the electroactive species flow toward the electrode. Therefore, the selected materials in these sensors must have a certain degree of permselectivity, so the flow caused by interferents can be hindered or lowered to some extent. A clear example of such a function is found in enzyme-based sensors (such as glucose sensors), where polymer materials are used as scaffolds for enzyme immobilization [1].

On the contrary, signals in implantable potentiometric sensors are generated by the transmembrane potentials associated with the concentration of the analyte. Therefore, the flow and consumption of electroactive analytes are not needed to function. In this type of sensor, the applied materials allow a fast setting of the transmembrane potential because of the interaction of the sensed ions and their ionophores.

3.2. Nanomaterial-Based Implantable Biosensors

It is shown that textured compositions are more suitable than smooth materials for enhancing the performance of biosensors in vivo applications due to vascularity improvement around the implant [48]. One of the well-described examples is incorporating a textured angiogenic layer over an implantable glucose sensor's surface [49]. It is believed that a different hydrophobicity and hydrophilicity of the materials prohibits the proteins or cells' adsorption over the surface. Another common phenomenon in in vivo biosensors is the clotting process caused by electrons exchange between blood proteins and cells on the implant surface (Figure 4) [50]. It is believed that the lower time constant of nanomaterials can decrease the clotting process when compared to metal-containing materials. However, the working mechanism of nanomaterials in in vivo systems is still debatable, but there are various studies where nanostructures used as an active material alleviate host body responses. Some of the regularly used nanostructures include nanoporous silicon [51], nanoporous titania [52], nanoporous carbon, etc. It is widely accepted that nanomaterials with controlled shapes and spaces can optimize drug delivery kinetics and improve anti-fouling characteristics [53].

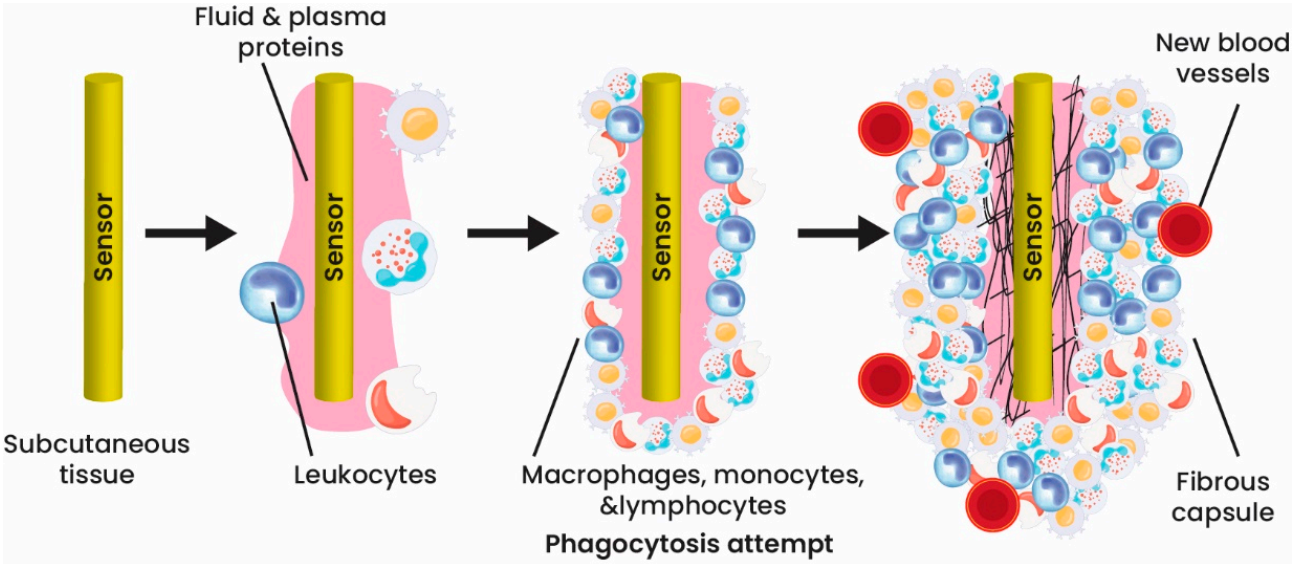

Figure 4. Formation of a fibrous capsule following the implantation of a biosensor in tissue.

As other important influencing factors, the permeability of the nanostructures is targeted in various studies. The output of these studies has led to the creation of nanoporous structures with smart responses to surrounding stimuli such as temperature, ionic strength, pH, and electromagnetic fields [54,55]. Although these nanostructures could effectively improve the performance of the sensors, integrating these materials in miniaturized implantables may be costly and difficult. To deal with this problem, polymer matrices embedded with nanomaterials became a type of nanocomposite coating that attracted a lot of attention from the researchers [56]. Table 2 shows the list of the reported nanomaterial-based implantable devices.

Table 2. Nanomaterials in the fabrication of implantable biosensing platforms.

Nanomaterial	Outcome	Ref.
Tunable gold nanogap	Ultra-sensitive electrochemical impedance biosensor for detection of streptavidin.	[57]
Si and Si/SiO_2	Round diaphragm pressure sensors.	[58]
Carbon nanofiber	Nano-implant for neural tissues monitoring, diagnosis, and treatment.	[59]
PbS hollow sphere QDs	Early-stage cancer diagnostics and treatment of ophthalmic diseases.	[60]
Ultrananocrystalline diamond	Implantable retinal microchip.	[4]
TiO_2 nanotubes	Soft-tissue responsive sensor.	[61]
BZT-BCT NWs/PDMs nanocomposite	Biodection of resistance with an implantable, wireless, and power-free nanosystem.	[62]
PLGA nanoporous Si composite	Bioresorbable sensor for the brain.	[22]

Si: silicon, SiO_2: silicon dioxide, PbS: lead sulfide, QDs: quantum dots, TiO_2: titanium dioxide, BZT-BCT: $Ba(Zr_{0.2}Ti_{0.8})O_3$-$(Ba_{0.7}Ca_{0.3})TiO_3$, NWs: nanowires, PDMs: polydimethylsiloxane, PLGA: poly(lactic-co-glycolic acid).

3.3. Fiber-Based Implantable Biosensors

As mentioned before, creating a steady interface between soft tissues and rigid biosensors is one of the grand challenges in implantable biosensors. Even though nanomaterials and nanotechnology could significantly deal with this problematic issue, there are still drawbacks and further work needed to fully resolve it. One of the practical and promising solutions is using flexible implantable fiber biosensors. For example, a mesh electrode prepared by following a thermal drawing procedure and materials (such as photoresist, gold, and polymer composite fibers) were successfully implanted in brain tissues and shown low immune responses with stable neural activity even after weeks from implantation [63]. In another study, silver nanoparticles and polyurethane were used to create an elastomeric fiber composite for the development of conductive and stretchable wireless system [64].

Fiber-based implantable biosensors present various advantages compared to the planar implantable sensing platforms, such as increased compatibility towards complex tissues and organs thanks to their one-dimensional (1-D) fibrous structure. Additionally, these devices are stitched on target organs directly which makes the surgical procedures simpler. Another point is that the system does not necessitate any welding which is known as a problematic issue for stretchable electronics. These systems also boast of having a passive readout circuit that can be expanded to a time-domain readout procedure due to the self-resonance feature of the circuit. Besides polymeric fibers, carbon nanotube (CNT) fibers (CNFs) have enhanced biocompatibility, flexibility, and wide surface areas (Figure 5) [65].

The flexibility of the 1-D fibers created an opportunity to develop spirally assembled multiple fiber electrochemical biosensors for the concomitant recognition of multiple molecules [65]. For example, the implantation of calcium ions (Ca^{2+})-glucose integrated fiber-based biosensors in a cat's vein exhibited promising results. This biosensor could record any fluctuation of Ca^{2+} and glucose in the blood. At the same time, the obtained information was timely and precise, which provides a potential in situ biosensor candidate

that is light and simple compared with the traditionally complicated sampling equipment and procedures [65].

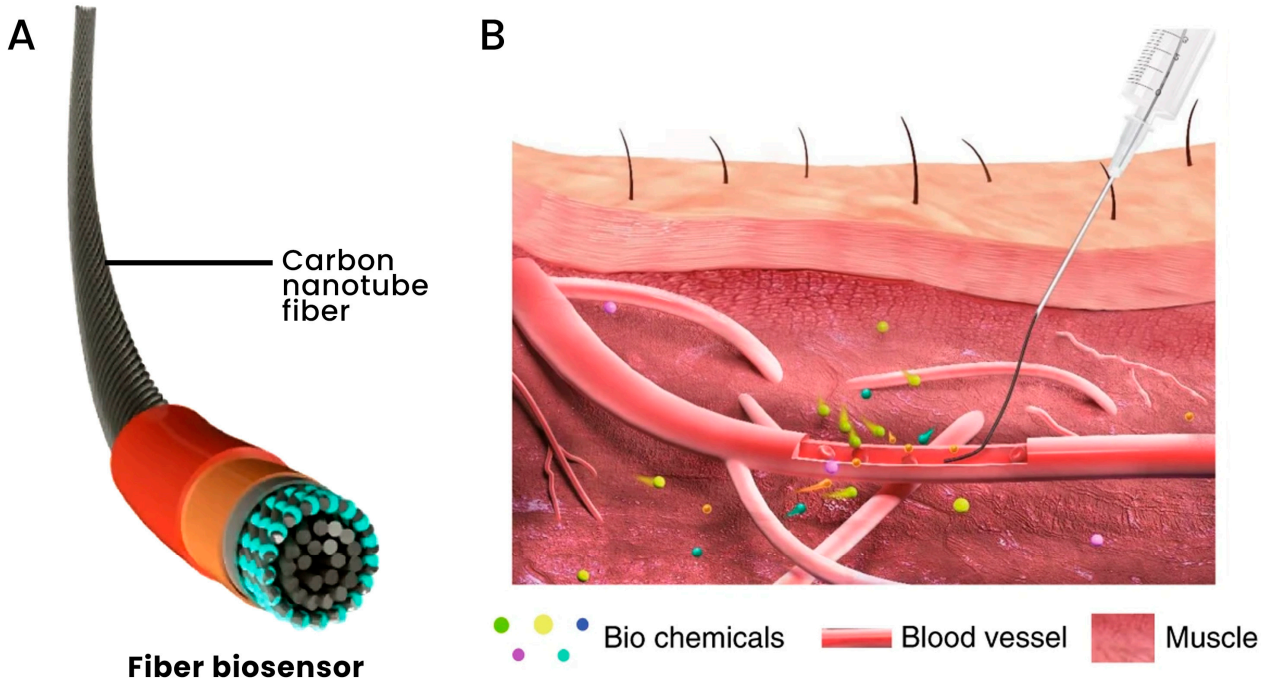

Figure 5. Carbon nanotubes (CNT) fibers-based implantable biosensor. (**A**) Structure of the CNT assembly and formation of the electrode with recognition and insulation layers. (**B**) Implantation of the CNT fiber-based biosensor for local monitoring. Reproduced with permission from ref. [65]. ©2020 Nature Publishing Group.

It is shown that the active surface area proportionally declines with increasing flexibility and decreasing size, which are unavoidable factors in developing novel implantable devices. The decrease in the surface area leads to an impedance increase and decreased signal-to-noise ratios which automatically decrease the sensing performance of the system [66]. One of the approaches to improve the sensitivity and limit of detection (LOD) in fiber-based implantable biosensors is the use of organic electrochemical transistors (OECTs), which can magnify the signals in contact with their targets [67]. Nevertheless, OECTs for in vivo applications are scarce given the mechanical incompatibility between OECTs and organ tissues. To overcome this lack, all-in-one structured OECTs were proposed (Figure 6A) [67]. All fiber OECTs can detect different chemicals, including dopamine (Figure 6B) and glucose (Figure 6C). Moreover, the fiber OECT's ability for in vivo monitoring was examined by implanting a platform in a mouse brain where the fluorescent images after 7 days of implantations demonstrated no noticeable immune reactions (Figure 6D–G).

The CNF materials cannot be implanted in the body without any supporting layer due to their soft nature. The use of rigid auxiliary materials is another approach to overcome the instability of soft fiber materials in in vivo applications. However, these materials can produce further tissue damage during removal due to micromotions of the soft biosensor and the lengthy removal procedure. Still, they are indispensable for implanting flexible biosensors [68]. To use the advantage of both soft and rigid materials in implantable sensors, microfiber neural probes (MFNPs) were introduced. MFNPs are core-shell structures with three layers comprising alterable, insulation, and soft neural layers (Figure 7) [68]. MFNPs can create environments similar to biological tissues, with the ability to be three-dimensionally folded, bent, or wrapped to form various shapes after contact with liquids. Therefore, dry-MFNPs could be directly implanted, and the wet-MFNPs, by absorbing water in implanted tissues, can later form stable interfaces with dynamic tissues [68]. Therefore, MFNPs are good systems that can be used to implant soft biosensors.

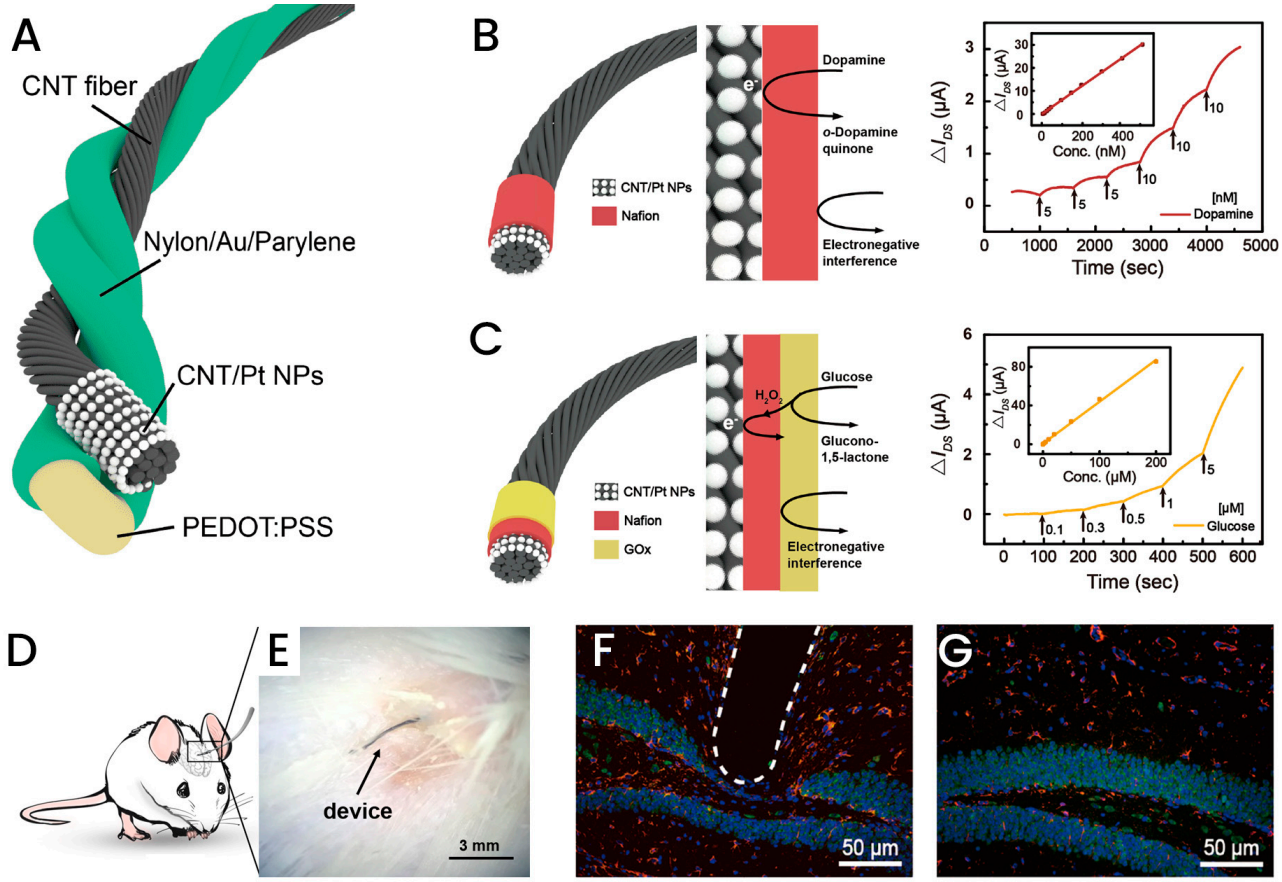

Figure 6. Fiber OECTs for biochemical detection of dopamine and glucose. (**A**) Representation of the OECT composition. (**B**,**C**) Example response towards dopamine and glucose. (**D**,**E**) Photograph of the OECT implanted on a mouse brain. (**F**,**G**) Demonstration of the OECT insertion in the brain followed through fluorescence staining. Reproduced with permission from ref. [67]. ©2020 Science China Press and Springer−Verlag GmbH Germany.

3.4. Polymer-Based Implantable Biosensors

The incredible nature of polymers has made them promising materials to deal with the complexity of physiological environments, where mutual interferences happen between tissues or organs and the implanted sensors. The ability of the polymer-based implantable sensor to respond to different physiological stimuli is an outstanding achievement in design and health monitoring. Based on the type of stimuli, polymer-based implantable sensors can be classified as biophysical (responsive to physical information such as pressure and temperature) and biochemical (real-time monitoring of molecular concentration such as sugar, ions, etc.) sensors. For example, Curry et al. described the application of a polymeric composite consisting of a molybdenum electrode with piezoelectric poly (L-lactic acid) nanofibers (PLLA) encapsulation for the creation of a nanofiber-based piezoelectric transducer [69]. Piezoelectrical transducers are widely employed in the development of pressure sensors. This smart composition generates electricity following the distortion of the structure. After implantation into the abdomen, a miniature circuit board (PCB) is linked via the piezoelectric PLLA-molybdenum nanofiber. Afterwards, the sensor self-degrades with time. As a response to insulated saline solution into the abdominal cavity and, consequently, internal fluid pressure, the sensor generates a wireless signal that can be read in response to the depression and relaxation of the abdomen (Figure 8A,C).

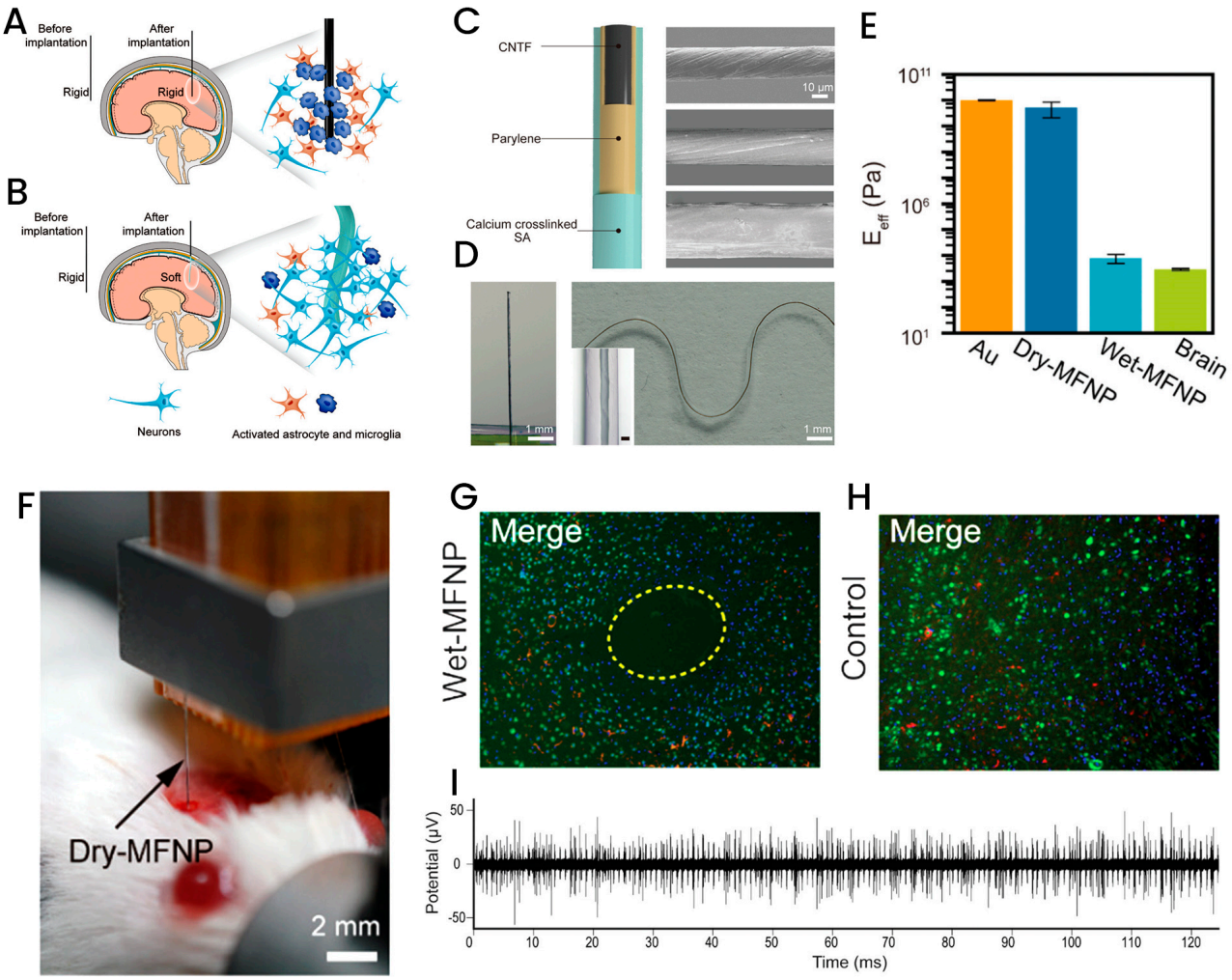

Figure 7. Implantable MFNPs-based module as an electronic interface for brain sensing. (**A**,**B**) Comparison between direct implantation of a rigid probe and a soft MFNP module in the brain. (**C**) Demonstration of a dry−MFNP composition. (**D**) Picture a wet-MFNP. (**E**) Effectiveness of elastic modules (Au wire, dry−MFNP, wet−MFNP) and mouse brain via indentation measurement. (**F**) MFNP implantation in a mouse brain. (**G**,**H**) Immunohistochemistry analysis of brain tissues implanted with an MFNP compared to a control (no implant). The yellow dashed circle shows the position of the MFNP. (**I**) MFNP−based recording of endogenous activity. Reproduced with permission from ref. [68]. ©2020 The Royal Society of Chemistry.

Some reports about temperature sensors have been used for in vivo applications. For example, Kim et al. reported the application of a polymer-based thin-film transistor temperature sensor (TFT-TS) in measuring brain temperature to understand cerebral metabolism [70]. A combination of temperature and pressure sensors were used to assess the intracranial physiological status (Figure 8D,E). In this sensor, the bioresorbable PLGA and Si-NMs enhanced the sensor's biocompatibility allowing for a straightforward assessment of the brain status. In the meantime, a commercial thermistor closely recorded the brain pressure and temperature, and a typical intracranial pressure (ICP) monitor was positioned close to the degradable sensor. The obtained results of temperature and pressure were closely comparable to the commercial sensor (Figure 8F). This bioresorbable sensor was able to differentiate between anesthesia-induced temperatures decrease and increased temperatures related to waking up, similar to the data observed in intraparenchymal tissues (Figure 8G) [22].

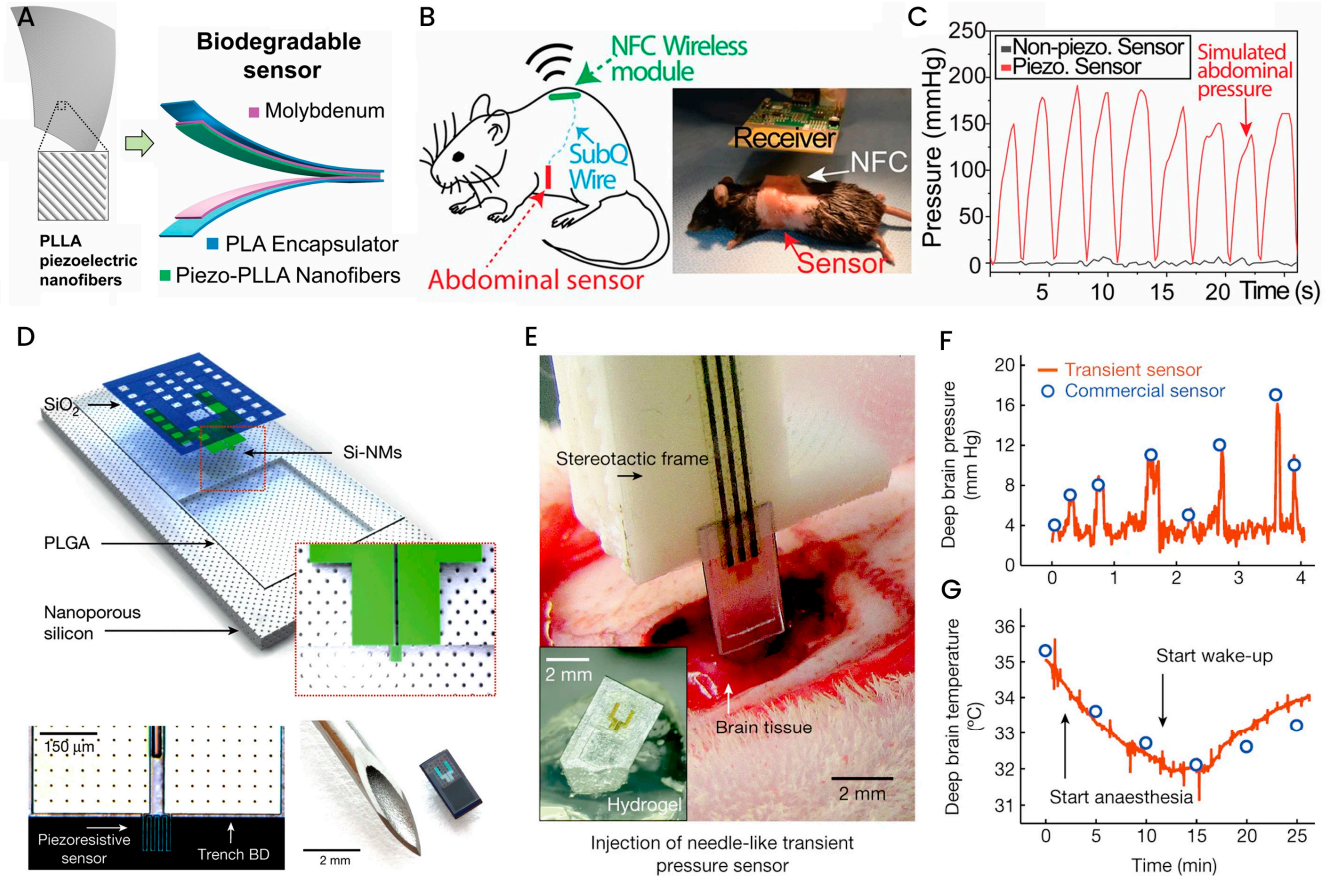

Figure 8. Demonstration of biophysical sensing using implantable biosensors. (**A**,**B**) Implantable piezoelectric device's structure and implantation in mouse abdomen. (**C**) Depressed and relaxed progression measurement of the pressure signal response [69]. (**D**,**E**) Structure of a piezoresistic device for the measurement of temperature and pressure and its implantation in the brain. (**F**,**G**) Data of the temperature and pressure collected by the device in comparison with a commercial sensor. Reproduced with permission from ref. [22] ©2016 Springer-nature Ltd.

As mentioned above, polymer-based implantable biosensors can be applied to detect biochemical substances which play essential roles in cellular activities. Rivas et al. generated an in vivo wireless and implantable electrochemical biosensor that can measure oxygen pressure in intramuscular tissues to distinguish between hyperoxic and hypoxic statuses (Figure 9A,B) [71]. Some abnormal mechanisms in the body can result in aberrant ion concentrations that change the local pH value. The pH changes can be used purposefully as indicators for metabolic conditions assessment. For instance, Dulay et al. created an implantable electrochemical pH biosensor based on polypyrrole's protonation/deprotonation process [72]. The insertion of this biosensor inside the leg muscles of 11 rabbits exhibited an excellent sensitivity with low variation between pH 4.0 and pH 9.0.

Moreover, enzyme-based transducers, considered the forerunners of the generation of implantable devices, are generally utilized for metabolism assessment of glucose detection [73]. Most commercialized implantable glucose biosensors are amperometric sensors that can detect products of glucose-enzyme reactions. The enzyme in this system is immobilized on the electrode surface to provide a redox reaction with an analyte and generate a current. Polymeric materials facilitate enzyme immobilization on the electrode surface either by chemically binding within the cross-linked polymer network or physically embedding within the materials. Other than immobilization, polymers can improve the sensitivity, biocompatibility, and lifetime of the biosensors. Additionally, Mimee et al. described an ingestible micro-bioelectronic device (IMBED) consisting of a probiotic sensor and ultralow-powered microelectronics [74]. This implantable biosensor is used to

detect gastrointestinal bleeding with its heme-sensitive probiotic component (Figure 9C). After bleeding, the released hem molecules from lyzed red blood cells can increase the hem extracellular concentration. The entrapment of heme by bacteria triggers luciferase operon luxCDABE expression, which generates light that can be detected by photodetectors incorporated in the device and translated as bleeding levels (Figure 9D). This study demonstrated the in vivo applicability of this device to detect blood signals (Figure 9D,E). In another study, Zhang et al. reported a polymer-based ratiometric electrochemical biosensor that can monitor the brain's copper ions (Cu^{2+}). The generation of reactive oxygen species (ROS) disrupts biological systems and upsets the balance of Cu^{2+} and Cu^{+} in the nerve center, leading to neurodegenerative disorders [75]. Xie et al. developed a platform for catecholamine neurotransmitters (CA-NTs) detection in rat brains. In the proposed platform, the polymeric composite polyethylene terephthalate (PET), platinum (Pt-GATE), and poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) were used as the active materials for covering the electrode surface (Figure 9F) [76]. The measurement of CA-NTs (dopamine, noradrenaline, and adrenaline) by the electrode (Pt-GATE electrode) is due to the oxidation of catechol groups in CA-NTs that generate Faradic currents (Figure 9G,H).

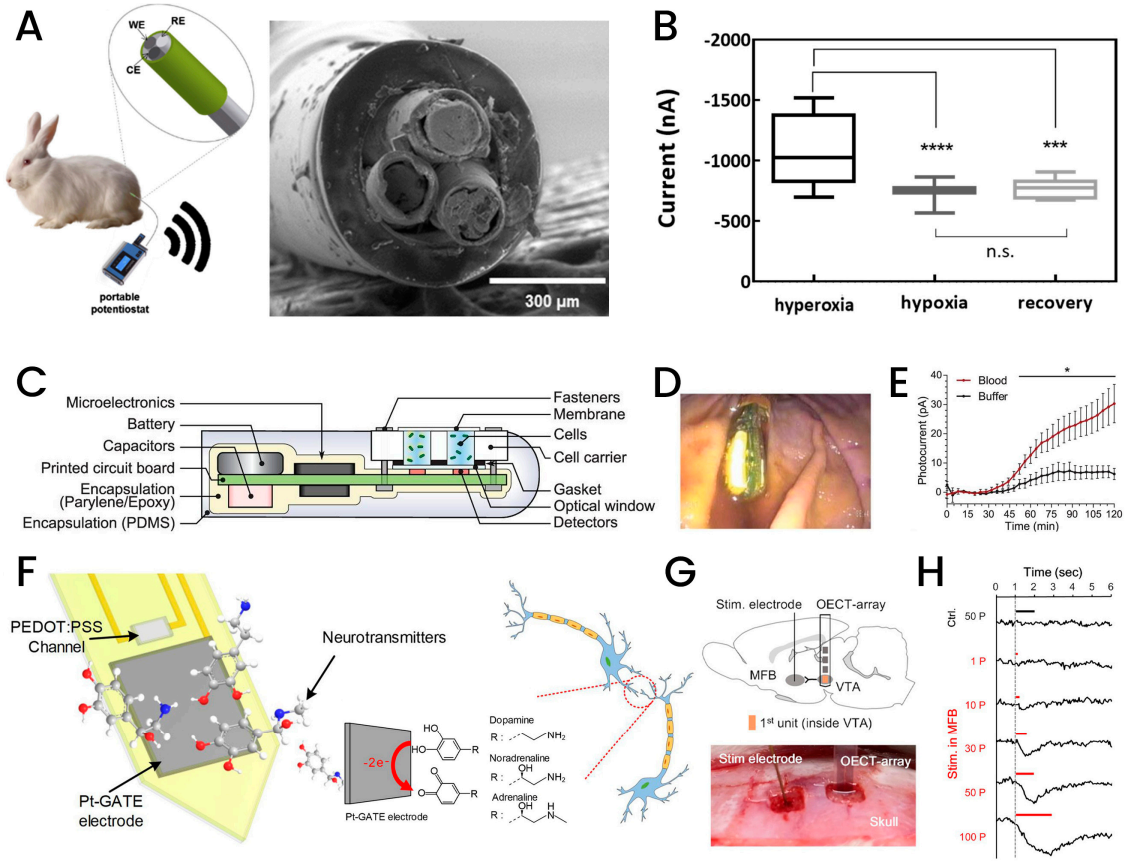

Figure 9. Typical applications of biochemical sensing via implantable biosensors. (**A**) Oxygen sensor implanted in a rabbit. (**B**) Data collected from the biosensor demonstrating the relation between the in−vivo oxygen status and cathodic current data. Reproduced with permission from ref. [71] ©2020 Elsevier. (**C**) Capsule−type biosensor composition. (**D**) Endoscopic view of the capsule in the rabbit's body. (**E**) Gastric bleeding sensing via the capsule−type sensor. Reproduced with permission from ref. [74] ©2018 AAAS. (**F**) OECT−array structure and CA−NTs detection principle. (**G**) Demonstration of the OCET array implantation. (**H**) Measurement of neural stimulation under different electrical pulses [76]. *, ***, ****, and n.s. correspond to statistical significance ($p < 0.05$, $p < 0.001$, $p < 0.0001$, and non significant) compared to specific group or a measurement time point.

4. Coating Implantable Biosensors

Foreign body reactions (FBRs) at the implant site is the main factor in losing the functionality of the implantable biosensors after insertion into the body [77]. The implantation of devices into the body causes tissue trauma, while the poor biocompatibility of the constructive materials causes biofouling, inflammation, and fibrous encapsulation. Thus, modifying the implantable biosensor to inhibit tissue reaction at the implant site is critical for biosensors in vivo applications. Polymers, including polyallylamine, pellethane™, polyethylene glycol, and horseradish peroxidase derivatives, are coating materials widely used for enhancing biosensors' biocompatibility and biodegradability due to the decrease in biofouling and FBRs [78,79]. For instance, Quinn et al. manufactured a copolymer composite from polyethylene glycol (PEG), 2-hydroxyethyl methacrylate (HEMA), and ethylene dimethacrylate for coating a glucose sensor [78]. The result of the biosensor's post-implantation demonstrated that the copolymer coating produces reliable sensitivities and less fibrous capsule formation after implantation, suggesting less of a foreign response reaction.

Unfortunately, coating materials cannot entirely omit the inflammatory response, and generally, anti-inflammatory drugs are prescribed to control the inflammation throughout the lifetime of the biosensors [80]. Chronic consumption of these drugs can produce some significant effects. Therefore, from this point of view, drug-loaded polymeric coatings can be the best solution. The hydrophilic nature of traditional polymeric coatings prevents direct drug loading in their structure. The synthesis of hydrophilic polymers could vastly overcome the lack of traditional polymers for the encapsulation of drug molecules, while the diffusion problems due to high hydrophobicity become the main obstacle to using them as coating materials.

Smart materials with the ability of fast analyte transmission to the sensing component and a controlled drug release during the lifetime of sensors are needed. Creating new coating materials for existing implantable biosensors is a lengthy and expensive procedure due to the need for an overall characterization, generation of a comprehensive understanding of the physicochemical features, and performing exhaustive toxicology studies. Thus, using existing materials and, more specifically, polymers is the logical strategy. Hydrogels (polymers with 3D structures) proved their ability as smart coating materials. For example, polyvinyl alcohol (PVA) hydrogels and PLGA microspheres permitted a fast influx of glucose via the hydrogel matrix combined with a gradual release of drugs from the microspheres [81]. An optimized smart polymer as a coating material should follow several critical features, including creating a uniform and homogenized structure with adequate adhesion over the sensor, long stability during the intended sensor life, and impact on the inflammation and vascularity of the surrounding tissues. Other than being biocompatible and anti-biofouling, hydrogels could show some merits, such as self-cleaning and thermo-responsiveness. For example, Ward et al. proposed a hydrogel membrane with the ability of self-cleaning and thermos-sensitivity that can be utilized as a coating material in implantable biosensors with long-term functionality [82]. This hydrogel consisting of poly (N-isopropylacrylamide) and embedded polysiloxane nanoparticles can serve as a thermo-responsive double network nanocomposite hydrogel (DNNC). Besides traditional coating materials, DNNC-based hydrogel membranes could swell and de-swell in response to local body temperatures at the implant site (Figure 10). Additionally, the DNNC hydrogel membrane exhibited low macrophage numbers after post-implantation, meaning the membrane causes macrophages' detachment. As a result, this biocompatible coating improves biofunctionality, allowing its application in medical implants.

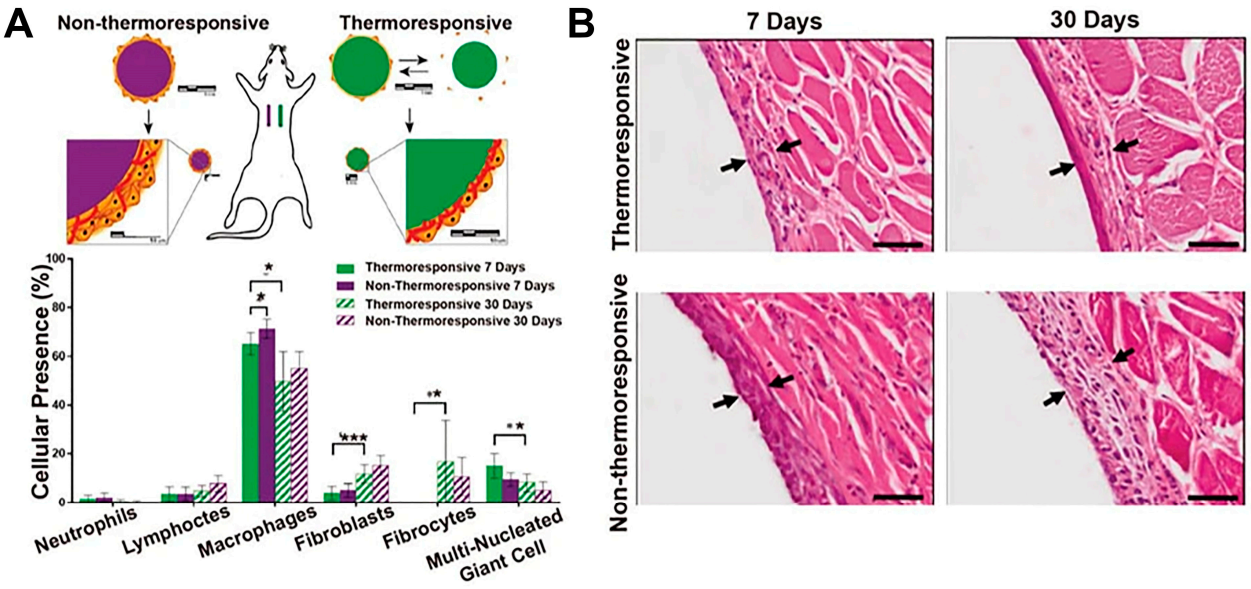

Figure 10. Schematic comparison between non-thermo-responsive and thermo-responsive hydrogels on immune cell response and fibrous capsule formation after 7− and 30−days post-implantation (**A**). *, ** and *** represent statistical significance ($p < 0.05$ $p < 0.01$ and $p < 0.001$). Various surface patterns of PDMS and their impact on macrophage number and capsule thickness between 2 and 8-weeks post implantation (the black arrows demonstrate fibrous formation) (**B**). Reproduced with permission from ref. [83]. Copyright © 2020, The Korean BioChip Society and Springer.

5. Challenges and Future Perspectives

Creating implantable biosensors comes with significant obstacles, including the foreign-body response, stability, and biosensor response, as well as the need for continuous monitoring, power supply, and data transmission. Overcoming these obstacles requires meeting specific criteria, such as utilizing more adaptable and biocompatible biomaterials, achieving miniaturization, and ensuring reliability. The implementation of these design parameters is essential in the development of implantable biosensors [84,85]. Some of the present and anticipated benefits of implantable biosensors for healthcare systems and the general public can be found in Table 3.

Various concerns should be considered and thought of in advance to design and then apply an ideal implantable biosensor. As aforementioned, biocompatibility of the design materials to avoid any unfavorable reactions in the body is the first and most crucial factor [86]. With developing science, many implantable sensors have shown minor cell injury. However, the materials used in long-term working biosensors (years or even a lifetime) must be biodegradable and biocompatible. For short-term strategies (e.g., digestible biosensors), high biocompatibility is demanded for both the instrument and the degraded products. In addition, some new synthetic biology and gene engineering strategies are being explored to generate biomolecule-based functional materials for the construction of the sensor. These techniques manipulate or mimic biomolecules to produce advanced functions. Additionally, the degradation of the implantable sensors can be controlled by following the manipulation processes theoretically inside cells.

Besides biocompatibility, the device should show lasting stability, accuracy, selectivity, miniaturization, downscaled power, and portability. The label-free electrochemical implantable biosensors with the promising features cited earlier have gotten tremendous attention in this field. Integrating nanomaterials and nanotechnology in the biosensor field could improve biosensors' performance and functionality and solve the main problematic issues in designing biosensors [87]. Many reports of in vivo biomedical devices are used for accurate, stable, simultaneous, and continuous monitoring. Developing a completely lab-on-chip system was a huge step toward creating wireless implantable biochip sensors [88].

Additionally, implantable bio-micro-electromechanical systems (bio-MEMS) could prove their in-situ monitoring ability of blood flow. Steeves et al. fabricated an intelligent and wireless bio-MEMS for non-invasive and early stenosis diagnosis in heart bypass grafts [89].

Table 3. Present and anticipated benefits of implantable biosensors for healthcare systems and the general public. Adapted from [84,85].

Aspect	Impact on Healthcare Providers	Impact on General Public
Daily monitoring of patients' physiology	By receiving daily information on patients' physiology, practitioners can decrease the volume of patients at congested hospitals and health centers while diagnosing health conditions at an earlier stage.	Implantable biosensors can provide people with firsthand knowledge of which specific behaviors could adversely impact their health, leading to increased self-awareness and behavioral change.
Personalized medicine	The collection of patient information from biosensors would enable patient stratification, leading to more effective treatments and facilitating the creation of a predictive, preventive, and participatory medical follow-up system.	The discovery of more efficient medical treatments based on patients' physiological, genetic, and demographic characteristics through the use of implantable biosensors would result in better healthcare outcomes.
Big data analysis	The patient information gleaned from biosensors could be utilized for big data analysis, where variables such as socio-demographics, medical conditions, genetics, and treatments would be scrutinized, leading to the identification of new trends.	Better understanding of the relationship between lifestyle and health.
Feeling of control	Implantable biosensors can empower individuals to take charge of their health, thereby reducing their stress levels, a known contributing factor to various chronic conditions.	Improved mental health and wellbeing.

Despite this achievement, the accurate evaluation of health status requires the detection of more health-related biomolecules as targets. In this case, optimal interactions between the probe and the targeting biomolecules with better anti-fouling is needed for the development of an ideal sensing interface. For instance, a biomolecule may function as a sensing layer, and a detection probe or an implantable biosensor may have multiplexed array constructions. In addition, developing multiplexed arrays of nanosensors that are responsive to a set of targets (molecules, viruses, enzymes, and chemicals) is an outstanding achievement in creating the next generation of implantable biosensors. Each array can be dedicated to one particular target in this complex design, while different targets can be assayed simultaneously. Many scientists welcome the idea of a moving implantable sensor where the unit is guided by remote controlled motion to reach its targeted site after implantation and finally generate the desired signals.

To apply implantable biosensors in actual clinical use, the device must satisfy the strict and conversive protocols arranged by governments. The FDA categorized implantable biosensors as class III devices that are meant for life-sustaining treatment or treating health disorders, including drug delivery systems or stents. To meet all the necessary criteria, uniformity, reproducibility of functionality, long-standing reliability, and safety ought to be investigated exclusively before clinical use. Unfortunately, there are no standard protocols or guidelines to test all the mentioned parameters due to the different applied standards for various devices and their related treatments. Therefore, multidisciplinary collaborations between scientists, medical doctors, and engineers are required to define the most suitable diseases to be targeted by implantable instruments and how to proceed for delivering the optimal treatment. Such collaborations can open the window to discovering innovative ideas for treatment approaches combined with developing implantable devices as a revolution in medical treatment.

6. Conclusions

In conclusion, technological advances in different fields, including nanomaterials and nanotechnology, biocompatible and biodegradable material developments, bioengineering and wireless power supply, and miniaturization techniques have led to numerous research focusing on implantable biosensors. These multi-task devices can significantly enhance society's quality of life by continuously monitoring patients' health status, reducing invasive interventions, and facilitating drug administration at specified times. Moreover, constant access of implantable biosensors to the health status of the patients in real time could lead to novel drugs and diagnostics development. However, it is evident that the science community, hospitals, and industry need to strengthen their bonds even further for such a considerable purpose.

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