

## Review

# Implantable and Semi-Implantable Biosensors for Minimally Invasive Disease Diagnosis

Yameng Xu <sup>1,2</sup>, Jingyuan Zhang <sup>2</sup> , Wilson Z. Ray <sup>2,\*</sup> and Matthew R. MacEwan <sup>2,\*</sup><sup>1</sup> The Institute of Materials Science and Engineering, Washington University, St. Louis, MO 63110, USA<sup>2</sup> Department of Neurosurgery, Washington University School of Medicine, St. Louis, MO 63110, USA

\* Correspondence: rayz@wustl.edu (W.Z.R.); macewanm@wustl.edu (M.R.M.)

**Abstract:** Implantable and semi-implantable biosensors fabricated with biodegradable materials and nanomaterials have gained interest in the past few decades. Functionalized biodegradable materials and nanomaterials are usually employed to satisfy clinical and research requirements because of their advanced properties. Novel fabrication techniques were developed to improve the efficiency and accuracy. Different working mechanisms were facilitated to design different types of sensors. This review discusses the recent developments of implantable and semi-implantable biosensors. The materials and fabrications are browsed, and different types of biomedical sensors for different variables are discussed as a focused topic. The biomedical sensors are discussed according to the targets and working mechanisms, followed by a focus on the nervous system sensing to provide an inspiration that different variables can be studied simultaneously on the single system. In the end, challenges and prospects will be discussed. This review aims to provide information of materials, fabrication approaches, mechanisms, and the state of the art for inspiration in designing novel implantable and semi-implantable biomedical sensors for general diagnostic activities.

**Keywords:** implantable and semi-implantable biosensors; biodegradable materials; nanomaterials; fabrications; mechanisms and strategies



**Citation:** Xu, Y.; Zhang, J.; Ray, W.Z.; MacEwan, M.R. Implantable and Semi-Implantable Biosensors for Minimally Invasive Disease Diagnosis. *Processes* **2024**, *12*, 1535. <https://doi.org/10.3390/pr12071535>

Academic Editor: Enrico Marsili

Received: 28 June 2024

Revised: 17 July 2024

Accepted: 18 July 2024

Published: 21 July 2024



**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

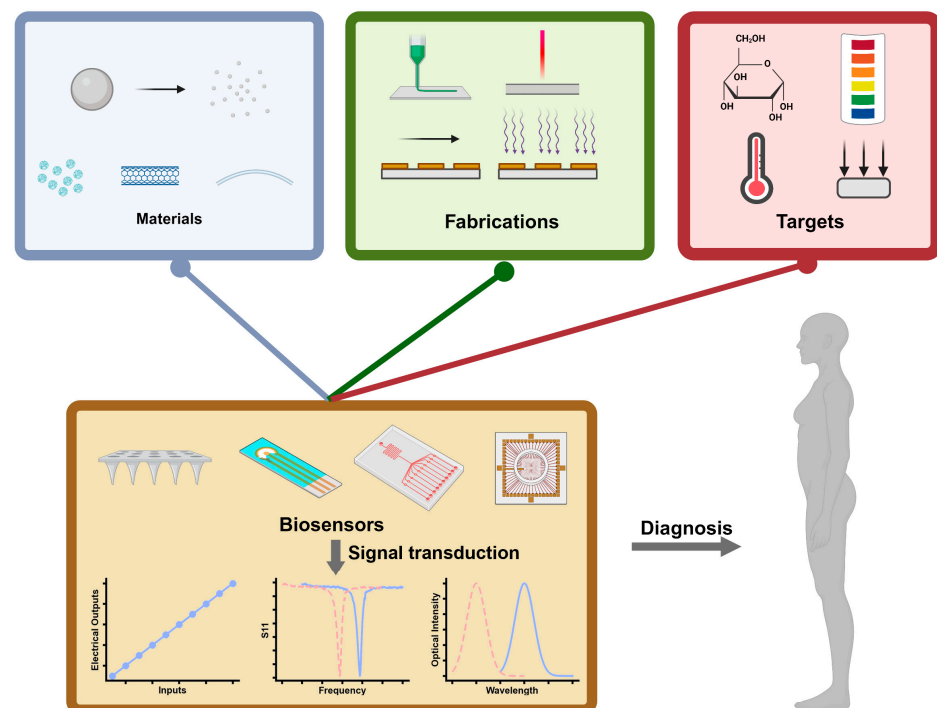
## 1. Introduction

Disease diagnosis is the first step in curative activities. However, traditional diagnostic equipment such as computed tomography (CT), magnetic resonance imaging (MRI), and X-ray machines are heavy, expensive, and inconvenient for patients due to tight schedules. To combat these issues, miniaturized biosensors have been developed. These small, portable devices can detect and measure biological information, allowing for portable or implantable diagnostic activities that reduce both time and expense costs.

Ayres has stated that the interactions between all physiological systems, particularly the neuroendocrine system and the hypothalamus, are crucial for maintaining robust health and physical strength. These interactions control physiological variables such as growth and development, macro/micronutrient and vitamin intake, socialization, thermoregulation, energy balance, oxygenation, detoxification, acid–base balance, and osmoregulation. Therefore, it is critical to sense and monitor changes in these factors to develop biosensing aimed at diagnosing diseases [1].

In the past few decades, implantable and semi-implantable biomedical devices have gained interest. Although quite a lot of wearable and benchtop sensors have been proven to work well, challenges include (i) only global information is provided; (ii) deep tissue monitoring may not be feasible; (iii) real-time monitoring may not be achieved; (iv) sufficient amount of testing targets may not easy to obtain; (v) contamination from environment can affect results; (vi) correlations between testing and desired targets need to be studied [2,3]. Thus, implantable and semi-implantable devices also have high clinical and biomedical values to overcome these limitations. Here, implantable biomedical devices

indicate those with full implantation, and semi-implantable devices may leave part of the units, such as control units [4], power units [5], and data collection units [6], outside the target tissues. There are several points to consider when designing such devices. The target tissues and factors are one of the essential considerations. Different tissues perform differently in mechanical properties, biological environments, and functions. For example, the modulus of the brain is only 0.1 to 10 kPa [7], while that for bone tissues can reach the level of GPa [8]. The pH of gastric juice is as low as  $\sim 1.0$ , while that of pancreatic juice is higher than 7.4 [9]. The nervous system transduces information by electrical [10] and chemical signals [11], respectively, so that electrical and chemical sensing are valuable to study. The selection of materials should suit the target tissues. For example, mechanical matching reduces injury and pain for patients and decreases the risk of functional loss of devices [12]. The working mechanisms should be selected wisely according to the environment of targets and the distance between the working site and the signal-receiving site to ensure the reliability of diagnosis and monitoring. Functionalized biodegradable materials and nanomaterials are usually employed because of their advanced properties to satisfy these points. Biodegradable materials eliminate the secondary surgeries to remove devices, and the adjustable properties allow devices to match the environment around the target tissues. Nanomaterials, due to their unique properties, perform high advantages in molecule binding, mechanical property modification, and functional enhancement [13–15]. Paralleled with material selections, the structures and sizes of implantable devices should be designed accordingly, especially considering the working environment. For instance, cardiovascular devices need to be miniaturized with a low profile to avoid impacting blood flow and arterial walls [16]. Deep tissue sensors can be designed as needle-shaped [17,18] to deliver the functional units deep enough with minimal injury to the patients. Fabrication approaches should be chosen according to the properties of the materials and the resolution requirements for the micro and nanoscales of the devices. In general, the design of biosensors should consider (i) materials, (ii) fabrication approaches, and (iii) targets to realize successful signal transduction and eventually perform accurate and effective diagnosis for patients (Figure 1).



**Figure 1.** Schematic diagram of factors for biosensor designs.

To provide recent information about materials, fabrication approaches, and the state of the art of implantable and semi-implantable biomedical devices, and give inspiration for novel biosensor development, we discuss the latest advancements in associated aspects in this review. The first section summarizes materials and manufacturing processes, followed by a discussion of various types of biomedical sensors that measure different variables such as chemicals, pH, temperature, and mechanics. We also focus on the sensing of the nervous system to demonstrate that multiple variables can be studied simultaneously using a single sensing system. Finally, we discuss the challenges and prospects for these biosensors.

## 2. Materials and Fabrications

The selection of materials is a crucial aspect when it comes to developing biosensing devices. To ensure the success of a biosensing device, it should meet certain clinical requirements, including (i) precise and efficient functionality; (ii) mechanical compatibility with targeted tissues to minimize tissue injury and device damage; (iii) biocompatibility with minimal invasion; and (iv) simple and cost-effective fabrication [19,20]. Several approaches have been developed to meet these requirements. For instance, soft and biodegradable materials were used to reduce mechanical mismatch with soft biological tissues and further minimize the need for secondary surgeries. Changes to material surfaces and the use and fabrication of nanomaterials have also been developed to improve accuracy and effectiveness. This section will discuss the selection of materials, followed by an introduction to advanced fabrication methods.

### 2.1. Biodegradable Materials

#### 2.1.1. Metals and Inorganic Materials

Metals have desirable electrical properties and expansion abilities, making them useful for creating thin film electric elements such as conductors, transistors, diodes, inductors, and capacitors [21]. In the past two decades, biodegradable metals such as magnesium (Mg), molybdenum (Mo), zinc (Zn), and tungsten (W) have been used to fabricate biosensing devices. As these metals undergo hydrolysis processes after being implanted, they can react with water and oxygen to produce dissoluble products in biofluids, which can then be excreted from the body [22,23]. The dissolution rate of different metals varies. Among them, Zn shows the fastest dissolution in PBS while others show relatively slower dissolution rates ranging from tens of micrometers per day to several nanometers per day [23]. The dissolution rate can be influenced by the pH of the surroundings. W shows a quicker dissolution rate with a pH of 5 compared to a pH of 7, while Mo shows the opposite performance. The rate of dissolving metals is also affected by the presence of proteins, and ions can speed up the dissolving process of materials like Zn, Mg, and Mg alloys [21,24], while the presence of ions can reduce oxygen solubility, which in turn slows down the rate of Mo dissolution, since Mo dissolution is linked to oxygen solubility [23]. Table 1 lists the electrical and dissolution properties of commonly used biodegradable metals, and their related applications.

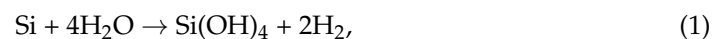
**Table 1.** Electrical and dissolution properties and applications of commonly used biodegradable metals. N/A, not applicable.

| Material       | Electrical Property            | Dielectric Constant ( $K_{sp}$ )                                                 | Dissolution Rates (nm/h)                                   | Dissolution Product          | Applications                       |
|----------------|--------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------|------------------------------|------------------------------------|
| Magnesium (Mg) | Conductor (interconnects) [19] | $8.9 \times 10^{-12}$ [25]                                                       | 70 (in Hank's solution [22] and PBS (pH 7.4; 37 °C)) [26]. | $Mg(OH)_2$ [27]              | Biodegradable battery system [28]. |
| Iron (Fe)      | Conductor (electrodes) [19]    | $1.8 \times 10^{-15}$ ( $Fe(OH)_2$ ) & $4.0 \times 10^{-38}$ ( $Fe(OH)_3$ ) [25] | 3.0 (in PBS (pH 7.4; 37 °C)) [26].                         | $Fe(OH)_2$ & $Fe(OH)_3$ [27] | Cerebral dopamine monitoring [29]. |

Table 1. Cont.

| Material        | Electrical Property            | Dielectric Constant ( $K_{sp}$ ) | Dissolution Rates (nm/h)                                          | Dissolution Product | Applications                                                        |
|-----------------|--------------------------------|----------------------------------|-------------------------------------------------------------------|---------------------|---------------------------------------------------------------------|
| Zinc (Zn)       | Conductor (electrodes) [19]    | $4.5 \times 10^{-17}$ [25]       | 7 (in Hank's solution) [22]; 146 (in PBS (pH 7.4; 37 °C)) [26].   | $Zn(OH)_2$ [27]     | Subcutaneous glucose monitoring [4].                                |
| Molybdenum (Mo) | Conductor (interconnects) [19] | N/A                              | 0.3 (in Hank's solution) [22]; 0.8 (in PBS (pH 7.4; 37 °C)) [26]. | $H_2MoO_4$ [27]     | Nitric oxide monitoring [30]; Biodegradable battery system [28].    |
| Tungsten (W)    | Conductor (electrodes) [19]    | N/A                              | 1.7 (in Hank's solution) [22]; 6 (in PBS (pH 7.4; 37 °C)) [26].   | $H_2WO_4$ [27]      | Subcutaneous glucose monitoring [4]; Wound healing monitoring [31]. |

Silicon (Si), a well-known semiconductor, is also bioresorbable as it dissolves following the reaction



where  $Si(OH)_4$  can further form a natural component of biofluids,  $[SiOx(OH)_{4-2x}]_n$  [22,32]. Factors to influence dissolve rates have been conducted on Si [23]. In an alkaline environment, Si dissolves at a faster rate. Due to the protein adsorption on the Si surface, and its limitation on water diffusion, Si shows relatively slower dissolution with higher protein concentration. Nevertheless, the addition of divalent cations such as calcium ions ( $Ca^{2+}$ ) and  $Mg^{2+}$  will promote the Si dissolution by increasing the deprotonate surface silanol groups and enhancing the water–siloxane reactivity.

### 2.1.2. Organic Materials

Inorganic materials are satisfying in performing as functional elements; however, there might be problems. For instance, their mechanical properties are quite different from those of soft tissues. To prevent short circuits or device erosion, it is crucial to encapsulate functional parts. Organic materials, such as natural or synthetic polymers, elastomers, and hydrogels, have been used in various clinical applications, including sutures, stents, and tissue engineering scaffolds [33–37]. In the field of biomedical electronics, organic materials are usually considered as the encapsulations and protections with waterproof, mechanical matching, and so on [38–40], since many organic materials are hydrophobic, and the mechanical properties are closer to soft tissues. Other than encapsulation and protection layers only, organic materials can also perform functional roles with or without modification. Examples include electric units [41,42], stimuli detectors [43], drug delivery control [33], etc. The properties can be controlled by adjusting components as desired [43–47].

Silk-derived materials are a widely used type of natural material that offers excellent biocompatibility, avoids inflammation and foreign body reactions, interacts with chromophores, and has tunable degradation rates [48–50]. Regenerated silk has ideal piezoelectricity/triboelectricity [48,51] with a surface charge density of  $1.86 \mu C m^{-2}$  and an instantaneous electric power of 4.3 mW, showing potential for functional interfaces between targeted tissues and devices.

The range of synthetic organic materials for encapsulation is large, including poly lactic-co-glycolic acid (PLGA), poly( $\epsilon$ -caprolactone) (PCL), poly-L-lactic acid (PLLA), poly-dioxanone (PDO), and polyglycolide (PGA) [52]. The hydrophilic bonds overcome the swelling and water penetration [53]. Recently, advanced organic materials have been synthesized to enhance the performance and longevity of biomedical electronic devices. For instance, poly(glycolide-co- $\epsilon$ -caprolactone) (PGCL) improved the mechanical properties with high elongation-at-break ( $\sim 1300\%$ ) and toughness ( $75 MJ m^{-3}$ ) [33]. Other than substrate and encapsulation, some organic materials have great conductivity, tri-

boelectricity, and semiconducting performance. The maximum conductivity of poly(3,4-ethylene dioxothiophene) polystyrene sulfonate (PEDOT:PSS) with d-sorbitol as a dopant can reach  $\sim 600 \text{ S cm}^{-1}$  [33]; the hole mobility of it with gold (Au) electrode can reach  $\sim 0.21 \text{ cm}^2/\text{V}\cdot\text{s}$  [53]. Moreover, some organic materials can be utilized as fluorescent agents triggering fluorescence emission due to unsaturated conjugation and extended  $\pi$ -cloud architectures [54]. Table 2 shows electrical and dissolution properties of commonly used biodegradable organic materials and applications.

**Table 2.** Electrical and dissolution properties and applications of commonly used biodegradable organic materials. N/A, not applicable.

| Material                                     | Electrical Roles  | Dissolution Rates           | Applications                                                                            |
|----------------------------------------------|-------------------|-----------------------------|-----------------------------------------------------------------------------------------|
| Silk                                         | Insulator [55]    | 75% in 14 days [56].        | Oxygen monitoring [56];<br>Fibroin conductive composites [57].                          |
| Poly lactic-co-glycolic acid                 | Insulator [55]    | Degradation in 8 h [58].    | NOx gas monitoring [58];<br>Humidity monitoring [59].                                   |
| Poly(lactic acid)                            | Insulator [55]    | 11 h [60].                  | Concentration sensors, pH sensors [61];<br>piezoelectric film for electro sensors [60]. |
| Poly(glycerol-co-sebacate)                   | Insulator [55]    | 80% in 35 days [62].        | Conductive patches in infarcted<br>myocardium [63].                                     |
| Poly( $\epsilon$ -caprolactone)              | Insulator [55]    | Degradation in 15 h [29].   | Cerebral dopamine monitoring [29].                                                      |
| Poly-L-lactic acid                           | Insulator [55]    | 56 days in 74 °C PBS [64].  | Piezoelectric force sensors [64].                                                       |
| Polydioxanone                                | Insulator [55]    | 10% in 55 days [65].        | Sensors membranes [66].                                                                 |
| Polyglycolide                                | Insulator [55]    | 17% to 40% in 55 days [67]. | Glucose monitoring [68];<br>Leptin monitoring [69].                                     |
| Poly octanediol-co-citrate                   | Insulator [55]    | Degradation in weeks [70].  | pH monitoring [70].                                                                     |
| Poly(glycolide-co- $\epsilon$ -caprolactone) | Insulator [33]    | 12 weeks [33].              | Encapsulation layers [33];<br>Synthetic molecular recognition [71].                     |
| Melanin                                      | Conductor [33,55] | N/A                         | pH monitoring [72];<br>Glucose monitoring [73].                                         |

Hydrogels were confirmed with (i) reliable and controllable mechanical properties, (ii) accommodation of molecular transportation, and (iii) reactions with biological substances [74]. These unique characteristics make hydrogels a promising material candidate for use in biomedical electronic devices in biosensing and responsive applications. Single-network hydrogels cannot stand high mechanical loads and deform heavily, especially with cracks or notches. Tough hydrogels with high mechanical performance are specifically synthesized with an energy dissipation network [54,75–80] or highly entangled network [81]. For example, the alginate/polyacrylamide hybrid gel can be stretched to 20 times longer without rupture, and the fracture energy is  $\sim 9000 \text{ J m}^{-2}$  [78]. The highly entangled double network (HEDN) hydrogels made of the polyacrylamide/poly(2-acrylamido-2-methyl-1-propanesulfonic acid)/poly(acrylic acid) system perform a fracture energy of  $8340 \text{ J m}^{-2}$  [81]. Hydrogels can also be synthesized with additional properties, such as stimuli-responsiveness, self-healing, antibacterial properties, adhesion, and more. This provides the ability to function as both functional and assistant units in biosensing devices. For example, crystalline domain cross-linked polyvinyl alcohol (PVA)/ $\text{Ca}^{2+}$ -cross-linked alginate shows an ionic conductivity of  $1.70 \text{ S m}^{-1}$  [76]. The reactions between primary amine groups with carboxylic acid groups, along with physical chain entanglement, make the polyethylene glycol-lactide acid diacrylate (PEG-LA-DA)/sodium alginate/chitosan network realize robust bonds on biological surfaces [82]. By synthesizing hydrogel systems with various monomers, they can respond and expand in different pH environments [9]. Additionally, nanomaterials can be added into nanocomposite hydrogel systems to en-

hance mechanical performance and introduce special functionalities, which will be further discussed in the following sections. The electrical and dissolution properties of hydrogel systems are listed in Table 3, as well as their applications.

**Table 3.** Electrical and dissolution properties and applications of representative hydrogel systems. N/A, not applicable.

| Hydrogel Material                                                           | Electrical Roles | Dissolution Rates                                        | Applications                                                             |
|-----------------------------------------------------------------------------|------------------|----------------------------------------------------------|--------------------------------------------------------------------------|
| Alginate/polyacrylamide                                                     | Conductor [83]   | 501 h at 80 °C, 50,000 ppm NaCl solution [84].           | Pressure sensors, strain sensors [84,85].                                |
| HEDN                                                                        | N/A              | N/A                                                      | Pressure sensors, strain sensors [81].                                   |
| crystalline domain cross-linked PVA/Ca <sup>2+</sup> -cross-linked alginate | Conductor [76]   | N/A                                                      | Soft adhesive interfaces for electrical sensors [76].                    |
| PEG-LA-DA/sodium alginate/chitosan network                                  | Conductor [82]   | 20 days to several months in PBS (pH 7.4) at 37 °C [82]. | Soft adhesive interfaces for optical, electrical, chemical sensors [82]. |
| Gelatin methacrylate (GelMA)                                                | Conductor [86]   | 2 to 7 h [87].                                           | Glucose sensors [86].                                                    |
| PEDOT:PSS/HPU                                                               | Conductor [88]   | 70% in 84 days [89].                                     | pH sensors [88].                                                         |
| PANI-PA/SPCE                                                                | Conductor [90]   | N/A                                                      | Vitamin C sensors [90].                                                  |
| PANI film doped with phytic acid                                            | Conductor [91]   | N/A                                                      | Electrical sensors [91].                                                 |

It is well known that the biodegradable ability of organic materials mainly relies on two different ways, hydrolysis, and enzymatic degradation, and most degradation rates of organic materials are controllable by adjusting the molecular weight, chain length, and synthesis conditions. Hydrolysis can be regarded as the decomposition reaction of compounds in water, and the process can be summarized as the following reaction formula:



CX is the compound participating in the reaction, and COH and XH are the products after the reaction [92]. Hydrolysis reactions usually require acids, bases, or enzymes as catalysts for organic compounds with macromolecular structures [93]. In the in vivo environment, organic materials are degraded mainly by enzymatic hydrolysis reactions using enzymes as catalysts. Depending on the composition of enzymes and organic materials, the pH value, temperature, and solvent composition of the environment in which organic materials are located will affect their degradation efficiency [94].

## 2.2. Nanomaterials

Nanomaterials have been a subject of interest for the past few decades due to their unique properties and strong structural stability. Unlike bulk materials, nanomaterials are very small, and range from 1 to 100 nm with a large surface-to-volume ratio, allowing for changes in properties through small modifications and bindings. The binding process could happen via covalent anchor groups, electrostatic interactions,  $\pi$ -stacking interactions, and other mechanisms [95]. The chemically tailorable physical and binding properties make nanomaterials a good choice for bioconjugation and cellular labeling [96]. Moreover, nanomaterials show advantages of high and broad adsorption, strong fluorescence quenching and oxidizability, high catalytic activity, and biodegradation [97]. Nanomaterials can be classified into four types: (i) Carbon-based nanomaterials, mostly shown in hollow lines, spheres, and other geometric shapes. This type includes materials such as diamond, carbon nanotubes (CNTs), carbon nanofibers, and graphene. (ii) Inorganic nanomaterials are metal and metal oxide nanoparticles (NPs) and nanosemiconductor materials. This type includes materials such as metal nanoparticles gold (Au) and silver (Ag), oxide nanoparticles ZnO,

and semiconductors such as silicon nanomembranes (NMs). (iii) Organic nanomaterials are mainly made of organic substances, such as dendrimers, micelles, liposomes, and polymer nanoparticles. (iv) Composite nanomaterials are multiphase nanoparticles in which one phase is composed of other nanomaterials or bulk materials. Such materials can be any combination of carbon-based, metal-based, or organic-based nanomaterials with any form of metal, ceramic, or polymer [98,99]. Some studies indicate that nanoparticles, like small Au NPs, can be directly phagocytosed by phagocytes [100]. On the other hand, some nanomaterials perform biodegradation, such as Si NMs, Zn NPs, and so on.

Surface plasmon resonance imaging (SPRi) is one of the most well-developed biosensing technologies. Such technology relies on the excitations of surface plasmons due to photon incident light [101]. However, detecting signals can be difficult due to the strict conditions required [101]. To overcome this challenge, metal nanoparticles are used due to their large surface area and high affinity with specific chemical groups [102]. They can also conjugate with specific molecules such as antibodies and enzymes, allowing them to act as molecular sensors and detect biomarkers [102,103]. Immobilizing enzymes onto nanosupports increases enzyme turnover and extends their lifetime [103]. Additionally, nanomaterials take part in multiple biological reactions, such as redox, where they mainly play the role of catalyst [29,104]. Other than sensing ability, some nanoparticles show potential for energy transfer as well. Recent examples include laser-induced heating of cholesteric liquid crystal (CLC) microdroplets [105] and pseudocapacitive nanoparticles to achieve energy storage [106]. On the other hand, nanomembranes may have the potential to serve as physical sensing and soft substrates. Si-based NMs are one family of the most popular nanomembranes. The properties of these nanomembranes have a sensitive responsibility to external physical stimuli. Thermal, temperature, and pressure may cause the shift of resonance peaks because of the thermal-optical effect and configuration change or resistance change following a linear relationship. After doping, Si NMs can serve as a semiconductor, transducing other signals, such as ionic current and transmitted light, into electrical signals, serving as recording electrodes [107] or photodetectors [6], respectively. Furthermore, because of their great flexibility and soft modulus, nanomembranes can serve as the substrate for implantable biological devices [16,29].

Nanomaterials are often integrated with other materials to realize free-standing ability and expansion of functionalization. As mentioned above, integrating nanomaterials with hydrogels forms novel hydrogel systems as nanocomposite hydrogels. For instance, the addition of nanofillers improves the mechanical properties of hydrogels due to the noncovalent interactions [75]; the deployment of nanoparticles brings remarkable adhesion ability [108]; the integration with fluorescent nanomaterials realizes robust sensing hydrogels [54].

Typically, the chemical properties of absorbable materials will cause some toxicity to biological tissues. However, it is worth noting that many studies have shown that the shape, size, and surface properties of nanomaterials may exacerbate their toxicity [109]. Among them, nanomaterials' small molecule size characteristics were found to affect the induction process of toxicity significantly [110]. Smaller nanomaterials exhibit higher toxicity than more significant nanomaterials, resulting in greater susceptibility to mitochondrial and lysosomal dysfunction, genotoxicity, cell cycle arrest, and apoptosis [111]. At the same time, multiple physicochemical properties of nanomaterials can cooperate with or antagonize each other, which makes it very difficult to verify the causal relationship between the toxicity of nanomaterials and their physical and chemical properties [109]. Therefore, the safety of absorbable materials using nanomaterials still needs to be carefully and responsibly evaluated.

### 2.3. Fabrications

Microscale devices can be fabricated through several techniques like transfer printing [112], physical vapor deposition [113,114], laser cutting [115], and additive printing [48]. With the development of new materials and applications for implantable biomedical devices, novel fabrication approaches are also emerging. Printing technologies are still one of the mainstream technologies. Digital printing techniques can be applied to inorganic and organic materials and nanomaterials. Paste-like materials, such as carbon and metals, can be screen-printed after being mixed with specific organic solutions, and organic solutions such as PEDOT:PSS can be inkjet-printed onto substrates to achieve fully printable devices. Several challenges should be addressed during device printing. The first challenge is the adhesion between ink and substrates. Fumeaux et al. modified PLA substrates with coating and oxygen plasma treatment to obtain an appropriate contact angle [41]. Another challenge comes from the electrical performance after printing. Fumeaux et al. modified PEDOT:PSS with dimethyl sulfoxide to increase cohesion and create PEDOT:PSS-rich domains [41]. However, there are some limitations to screen and inkjet printing. The resolution of screen printing is lower, with thicker depositions and required patterned masks. The viscosity of ink materials for inkjet printing is narrow, lower than that of polyimide [116,117]. Thus, Herbert et al. selected the aerosol jet printing (AJP) technique [16], which aerosolized functional ink and delivered it to the substrate via a carrier gas [118]. APJ is a printing technique with a wide range of ink selections (1 to 2500 cP of viscosities) without requiring mask fabrications. APJ realized rapid, high-resolution printing for both conductive nanoparticle inks and polymer inks for micro-scaled devices. Three-dimensional (3D) printing allows multi-material device fabrication, precise definition, and control of complex internal microstructures, so it is also widely used to fabricate biomedical devices [48,119–121].

In addition to simply digitally printing devices, some research has combined this with other technologies. Li et al. deployed hot-rolling and photonic sintering with screen printing [122]. Hot-rolling shrinks the volume of nanoparticles, therefore increasing the spontaneous bonding and enhancing the tunneling effect. They also developed a water-sintering technique that created a weakly acidic environment that released metal ions and allowed a galvanic reaction between Mo and W, redepositing Mo onto both Mo microparticles and W microparticles. These mechanisms improved the conductive properties of metal pastes [4]. Shou et al. demonstrated a technique using confined evaporation–condensation to mediate laser printing and sintering of Zn NPs [123]. They used high-speed laser scanning to form high-crystallinity Zn NPs while heating the Zn NPs into evaporation within a confined space. Oxide layers delayed the coalescence of Zn particles, and the evaporation of core dominated. When Zn vapor escaped through a confined gap smaller than 1  $\mu\text{m}$  and reached the cold substrate, no significant collisions with other atoms were observed. Thus, printing quality by this technique is similar to that by thermal evaporation under vacuum, increasing the conductivity.

Other than printing approaches, Yang et al. developed a new high-speed, scanned, picosecond-pulsed laser ablation approach for multilayered biodegradable devices [124]. Such laser ablation could achieve patterning, thinning, and cutting of defined geometries with high resolution and minimal damage to underlying layers, since all processes occur in a fast, dry process with minimal thermal load. It is a highlighted progress compared to the conventional laser cutting technique. The ablated thickness reduction can be precisely controlled by adjusting the average power, scanning speed, frequency, and the number of repetitions according to the target materials. The high speed of laser ablation ensures the limitation of thermal diffusive zones, reducing the overtreatment. As the proof-of-concept, biodegradable microvascular flow sensing probes, electrocorticogram (ECoG) recording electrodes, and cardiac monitoring systems were fabricated successfully with desired sensing functions.

Another novel fabrication technique was developed by Wu et al., named the sewing technique [125]. Compared with the traditional fabrication processes, the sewing technique avoids high temperatures and reactive solvents, which is a key improvement for bioresorbable device fabrications. Here, the biodegradable metal wire (W) serves as the bobbin, and the polymeric filament (PVA) serves as the needle thread. An interlocking stitch inside the hole created by the needle penetration can be made between the needle thread and the bobbin thread through the shuttle hook interlacing. Controlled by the specific software, desired geometries, automation, and high speed can be achieved. Defining proper thread tension is important to make sure that it does not tear through the edges of the holes, which will result in local plastic deformation. Using the sewing technique, they successfully fabricated stretchable interconnections, coil antennas, and stretchable wireless cardiac pacemakers.

### 3. Recent Developments in Implantable and Semi-Implantable Biosensing

Implantable and semi-implantable biosensors provide local information, especially for deep tissues, without environmental effects. In the past several decades, implantable and semi-implantable biosensors were developed to achieve various functions, including chemical, physical, and even biological information. In this section, different types of recently developed biosensors are introduced.

#### 3.1. Chemical and Biomarker Sensors

Chemical and biomarker sensing is one of the most direct approaches for physiological monitoring, achieving health status assessment, disease diagnosis, and postoperative intervention determinations [19]. Vital chemicals and biomarkers exist in biofluids, such as sweat, urine, blood plasma, cerebrospinal fluid, etc.

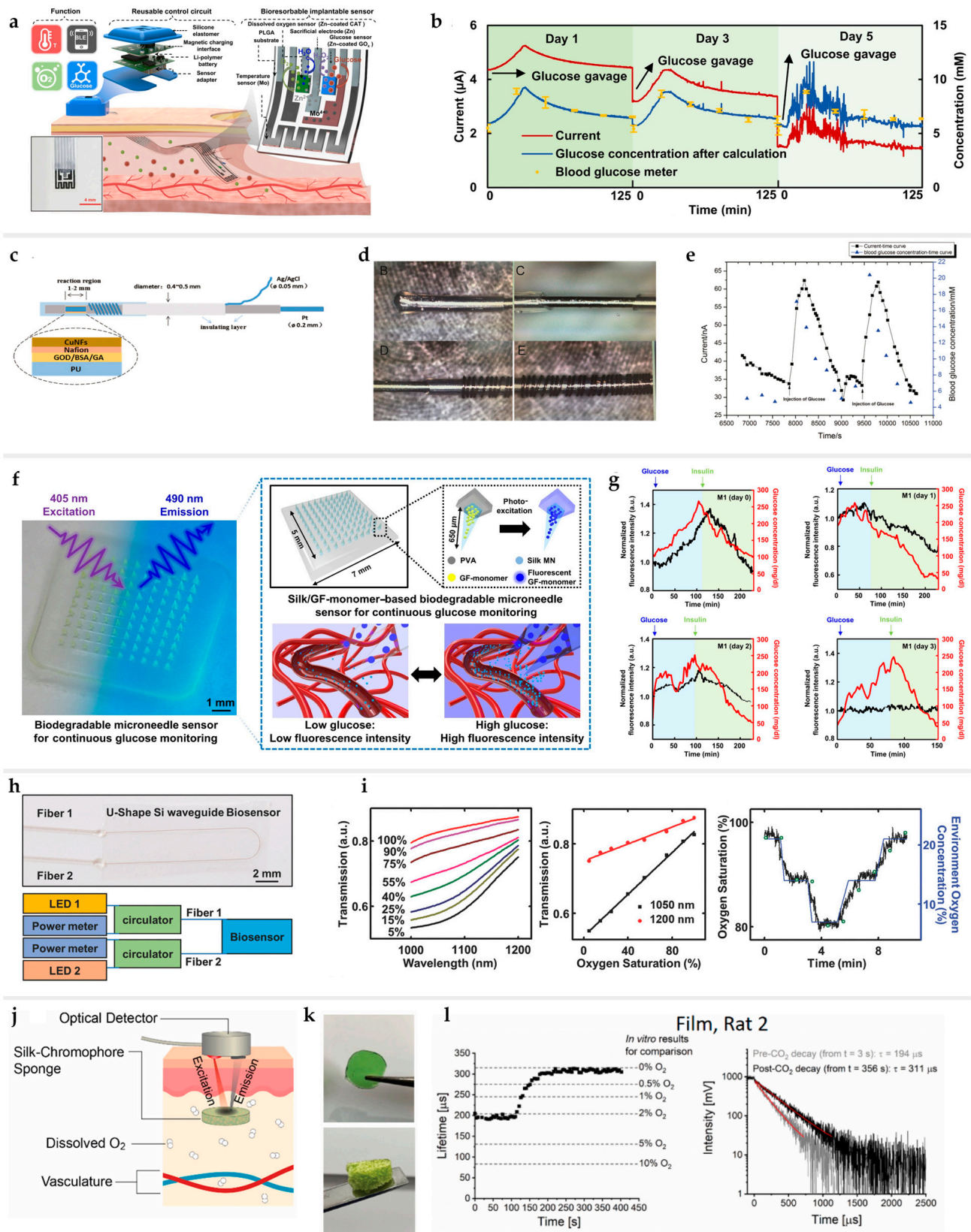
##### 3.1.1. Glucose Sensors

Glucose is one of the leading energy suppliers to humans. However, the cellular uptake or storage of glucose in patients with diabetes can be impaired. Patients with diabetes face a high threat to life. According to WHO, about 1.5 million deaths were directly caused by diabetes in 2019, and half of those occurred before the age of 70. Diabetes also causes complications such as kidney, cardiovascular diseases, and hypoglycemia, which could result in acute brain and heart damage [126].

Because of the reliability of glucose oxidation by glucose oxidase (GOx), most implantable glucose sensors are enzyme-based electrochemical sensors. This redox reaction produces hydrogen peroxide ( $H_2O_2$ ) and generates electrons, transferring the glucose concentration to measurable electrical signals. GOx can be directly coated onto working electrodes such as Zn [4] and carbon [49]. Molinnus et al. screen-printed carbon electrodes onto biodegradable and biocompatible fibroin substrates, assembled with GOx membrane, and realized glucose monitoring at 0.5 to 4 mM [49]. Their devices maintained the performance for up to around 1 year with negligible cross-sensitivity toward ascorbic acid, noradrenaline, and adrenaline. Similarly, Li J. et al. assembled Zn-working electrodes (Zn WE) coated with GOx, Mo-counter electrodes (Mo CE), and Mo-W reference electrodes (Mo-W RE) to achieve real-time glucose monitoring, as Figure 2a,b show [4]. The working period can reach 5 days in vivo by applying a sacrificial Zn layer. The sensing range of glucose concentration is 0 to 25 mM with a sensitivity of  $0.2458 \mu A/mM$ . Fumeaux et al. made some progress on organic electrochemical transistors (OECTs) with biodegradable materials, including PEDOT:PSS, carbon, and Zn [41]. The high surface area and good electron transfer of carbon allow such glucose sensors to monitor the glucose level at the range of 1  $\mu M$  to 1 mM with a sensitivity of  $-3.4 \pm 0.6\%/dec$ . To expand the potential of the glucose sensors, Luo et al. exploited a closed-loop diabetes minipad with hollow biodegradable microneedles, which integrate glucose sensing and insulin release [127]. They selected natural biodegradable materials, chitosan as the hollow microneedle array, and deposited Au and Ag as working and reference electrodes, respectively, with the

coating of GOx. Insulin was stored inside the hollow microneedles and electroosmotically pumped by polycarbonate film with nanopores. The needle array was inserted into the skin within 1 mm, which does not touch nerve endings and the capillary bed in the lower dermis. The sensor could sense the glucose concentration up to 20 mM with the sensitivity of 0.311  $\mu\text{A}/\text{mM}$ . Signals could be sent back to the control unit and lead to the insulin release. Nanomaterials improved the current captures when integrated with enzyme-based electrodes [103], and usually serve as the catalyst of oxidation of glucose by GOx since a large number of binding sites can be provided, as mentioned before [104]. Fang et al. designed microneedle electrodes made of copper nanoflowers, Nafion, GOx, and polyurethane (Figure 2c–e) [128]. The glucose sensors showed desired properties, with a sensing range of 0 to 20 mM and a sensitivity of 42.38 nA/mM. Jayakumar et al. employed multiwalled carbon nanotubes (MWCNTs) in the sensors, increasing the current density and surface coverage of enzymes or mediators [103]. As a result, their sensors had a 146% improvement in current density compared to the similar systems without nanomaterials. Xie S. et al. utilized the fluorescence quenching quantum dots (QDs) to detect glucose [54].  $\text{H}_2\text{O}_2$  can fluorescence quench specific QDs (CdSe/ZnS). The electron hole of QDs can serve as the acceptor and cause electron-transfer reactions with  $\text{H}_2\text{O}_2$ . The nonfluorescent CdSe anion thereby forms and decreases the fluorescent intensity of the QD-GOx. Specially, they developed a microfluidic method to fabricate water/oil/water droplets and polymerize them by UV exposure. Nanomaterials and organic solution containing photocurable polymers were injected into two separated tapered cylindrical capillaries as inner and middle phase, respectively. An aqueous solution with surfactant was injected in collection capillaries to form double emulsion drops and these were exposed under UV to form sensors.

Some nonenzymatic glucose-sensing approaches were also developed, converting glucose information into optical or fluorescence signals. Bai et al. used PLGA-encapsulated monocrystalline Si (m-Si) to realize continuous glucose monitoring [129]. Si has a high refractive index, so the optical mode confinement is tight at sub-micron scales. Light can be delivered to the target precisely at dimensions as small as a single cell. Near-infrared light absorbed by tissues produces spectral signatures because of the overtones and combinations of molecular vibrations from specific chemical groups, providing information about chemical composition. Their sensors successfully detected glucose concentrations as a function of optical returning loss due to chemical groups, especially at 1160 and 1330 nm wavelengths. The detection range is 120 to 180 mg/dL with a 15 mg/dL sensitivity. Sang et al. integrated biodegradable glucose-responsive fluorescent monomer (BGF) into silk microneedle arrays [3]. The novel BGF provides diboronic acid as the recognition site for binding glucose and anthracene, emitting fluorescence. When glucose binds with diboronic acid, the reaction between boron and nitrogen prohibits the photoinduced electron transfer and shows strong anthracene fluorescence (Figure 2f). The range of their sensors is 50 mg/dL to 450 mg/dL, and continuous monitoring can be satisfied, as Figure 2g illustrates. They further developed a user-friendly home diagnosis system by integrating a light source of 405 nm light-emitting diode array and a 450 nm optical long-pass filter with a smartphone. The system converted the fluorescence image to visible RGB signals that allow patients to analyze glucose levels easily.



**Figure 2.** Representative examples for chemical and biomarker sensors: (a–g) Enzyme-based electrochemical sensors. (a,b) Schematic illustration, photo and sensing results of the fully printed and self-compensated bioresorbable electrochemical devices based on galvanic coupling. From ref. [4]. © The authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license <http://creativecommons.org/licenses/by-nc/4.0/> (accessed on 25 June 2024). Reprinted with

permission from AAAS. (c–e) Schematic illustration, photo and sensing results of needle-type microelectrode for glucose sensing. Reprinted with permission from ref. [128]. Copyright 2018 Elsevier. (f–i) Optical-based chemical and biomarker sensors. (f,g) Photo, schematic illustration, and sensing results of the biodegradable microneedle sensor array. From ref. [3]. © The authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license <http://creativecommons.org/licenses/by-nc/4.0/> (accessed on 25 June 2024). Reprinted with permission from AAAS. (h,i) Photo, schematic illustration, and sensing results of the flexible transient optical waveguides and surface-wave biosensors constructed from monocrystalline silicon. Reprinted with permission from ref. [129]. Copyright 2018 Wiley-VCH. (j–l) Schematic illustration, photo and sensing results of bioresorbable lifetime-based phosphorescent oxygen sensors. Reprinted with permission from ref. [50]. Copyright 2023 Elsevier.

### 3.1.2. Sensors for Other Chemicals and Biomarkers

Mechanisms of chemical and biomarker sensors can be similar to those of electrochemical, optical, and fluorescent sensors. For instance, Mehrotra et al. demonstrated an electrode system to detect oxytocin [130]. They incorporated biodegradable chitosan with carbon nanofibers and functionalized WE with the antibody to oxytocin-neurophysin I. After trapping oxytocin molecules, the surface coverage of WE increases so that the resistance to electron transfer increases. Therefore, the charge-transfer resistance increases and can be measured with electrochemical impedance spectroscopy. The sensors are sensitive to detect oxytocin of  $24.98 \pm 11.37$  pg/mL with a sensitivity of  $2.77 \times 10^{-10} \Omega/\log \text{ ng mL}^{-1}/\text{mm}^2$ . Xu M. et al. designed a three-electrode sensor fabricated with only organic materials (organic electrodes, OE) [42]. They used PEDOT:PSS as the conductive unit and silk fibroin as the support substrate. OE can detect the current change due to the redox reaction between ascorbic acid and electrodes as a linear function with ascorbic acid concentration up to  $49.2 \mu\text{M}$ . The signals can be amplified since redox reactions happen on WE, CE, and RE simultaneously. After binding with antibodies, such as anti-VEGF165 antibodies, corresponding factors, such as VEGF, can be detected by electrochemical impedance spectroscopy since the resistance to electron transfer increases after the binding between antigens and antibodies [131]. Xie X. et al. developed a nanosensor that can monitor blood oxygen saturation and detect heparin by using gold nanorods (NRs) [132]. The absorption band of NRs changes due to the aggregation caused by the conjugation between the amine groups from heparin and NRs. Oxyhemoglobin ( $\text{HbO}_2$ ) and deoxyhemoglobin (Hb) have different absorption spectra, thereby the oxygen saturation ( $\text{StO}_2$ ) can be calculated by the ratio between the ( $\text{HbO}_2$ ) and total hemoglobin ( $\text{Hb} + \text{HbO}_2$ ) [133,134]. The m-Si-based sensors developed by Bai et al. (Figure 2h) can detect not only glucose but also blood  $\text{StO}_2$  by analyzing the absorption peak at 1050 and 1200 nm [129]. The transmission at both the two wavelengths shows a linear relationship with the  $\text{StO}_2$  and realizes continuous monitoring (Figure 2i). Similarly, Guo H. et al. developed a wireless implantable optical probe with two photodetectors [5].  $\text{StO}_2$  can be calculated by the light absorption coefficient at the emission wavelength (660 nm and 850 nm) based on the gradient of absorbance. They also designed biodegradable barbs by PLGA to ensure mechanical stability at the implantation site and safe post-operation extraction. Their probes provide satisfactory performance at the porcine flap and kidney model, with successful detection of ischemia and congestion status. These  $\text{StO}_2$  sensors show desired prospects to ensure smooth blood flow to succeed in flap and kidney transplantation and track the cardiopulmonary health of patients after cardiothoracic surgery [135]. In addition to  $\text{StO}_2$  measurement, Presley et al. developed a silk-chromophore oxygen sensor (Figure 2j) that provides another possibility for life-threatening disease [50]. They fabricated films and sponges with silk and Pd (II) tetramethacrylated benzoporphyrin (PdBMAP), as Figure 2k shows. PdBMAP is an oxygen-sensitive chromophore whose phosphorescence intensity is inversely proportional to the oxygen concentration as follows:

$$I_0/I = 1 + K_{SV}[\text{O}_2], \quad (3)$$

where  $K_{SV}$  is the Stern–Volmer quenching rate constant. They calibrated the phosphorescence decay curves with different oxygen concentrations and concluded Stern–Volmer plots of phosphorescence lifetime versus oxygen concentration. After that, they implanted silk-PdBMAP films and sponges into rodent models and realized continuous oxygen concentration monitoring (Figure 2l) for up to 4 weeks.

### 3.2. pH Sensors

Maintaining pH at homeostasis is vital for health. Imbalances in pH cause severe problems, such as ischemia, kidney disease, mental illness, etc. [136,137]. pH value can also indicate the health status. For instance, infections after surgery usually produce an acid environment that lowers the pH from 7.5 to 6.7 [138]. Lower pH may also suggest cancer [139] or cardiac disease [140]. Amsel’s criteria indicate that vaginal pH higher than 4.5 can be considered bacterial vaginosis [141]. Moreover, failure of gastrointestinal surgeries may cause anastomotic leakages, which change the abdominal pH values and affect other organs [142]. In this case, continuous real-time pH sensors call for interest in the field of implantable biomedical devices.

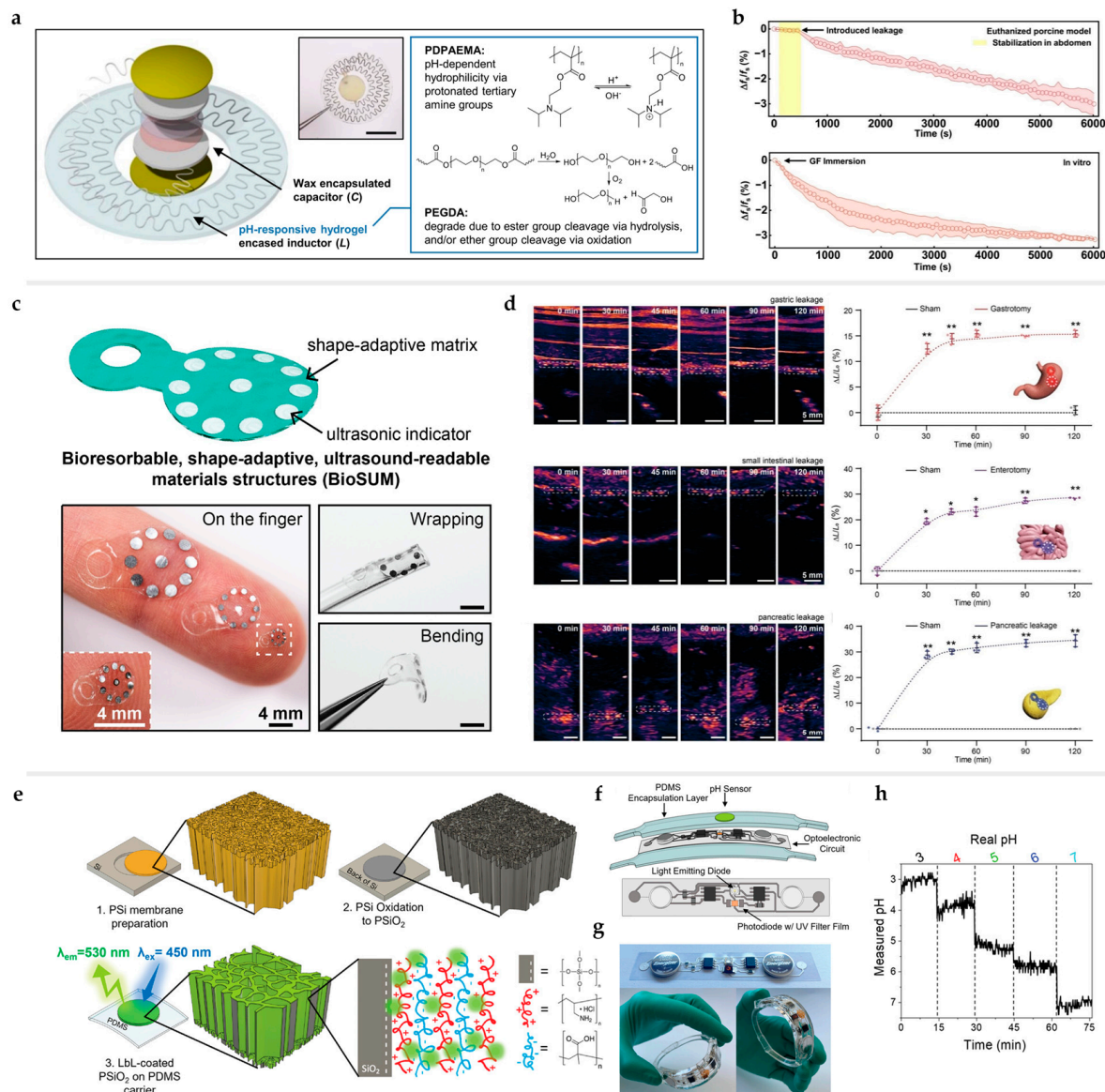
It is well known that pH values depend on the concentration of hydrogen and hydroxide ions. Different strategies are developed to measure their concentrations. One strategy is to convert ion concentrations to electrical signals. Nanomaterials are usually involved in such sensor designs. For instance, Chou et al. developed a flexible polypropylene micromembrane (PPMM) deposited with iridium(IV) oxide ( $\text{IrO}_2$ ) NPs [143]. The introduction of  $\text{IrO}_2$  brings pH response ability due to the redox reactions, and the pH values influence the redox potentials. They pointed out that their sensors can respond at the range of pH 2 to 12 with a sensitivity of  $-74.45 \text{ mV/pH unit}$ . Meanwhile, the sensor performed fatigue resistance within 5000 bending cycles and showed excellent biocompatibility. Ming et al. utilized the pH-dependent reversible charge transfer of PANI, decorating it with Au NP and platinum (Pt) black to increase the surface area and conductivity. The resulting sensor showed a sensing range of pH 4.0 to 9.0 with a sensitivity of  $-57.4 \pm 2 \text{ mV/pH unit}$ .

In addition to electrochemical methods, some hydrogels perform pH-responsibility. One example is polyacrylic acid (PAA)-based hydrogel. The presence of carboxylic acid side groups makes PAA hydrogel show volume change based on the pH of the surroundings. A high-pH environment deprotonates carboxylic acid groups, making it negatively charged as carboxylate ions [144]. Because of the increased electrostatic repulsions between bound charges, accompanied by osmotic pressure, the PAA hydrogel has a swelling behavior in the more alkaline environment [145]. Based on this mechanism, Wijayaratna et al. embedded a radiodense tantalum bead and tungsten wire at a specific length to monitor the pH-caused volume change on the hydrogel [138]. X-ray images can detect the change in the length and they showed a sensitivity of  $3 \text{ mm/pH unit}$  between pH 4 and 8. They attached such a pH sensor to an explanted prosthetic hip, therefore detecting the infection status by monitoring pH levels between 6.5 and 7.5. Li S. et al. designed a wireless passive gastric leakage detector [146]. They copolymerized 2-(diisopropylamino)ethyl methacrylate (DPAEMA) and poly(ethylene glycol)diacrylate (PEGDA) to form PDAEMA-PEGDA with the pKa (Ka is the acid dissociation constant) around 6.3, and embedded an inductive coil made of Zn, as Figure 3a shows. The protonated tertiary amine units cause protonation and, therefore, increase the electrostatic repulsive forces and osmotic pressure. After swelling in a low-pH environment, the inductive coil expands, and the inductance ( $L$ ) increases. The changes in resonance frequency ( $f_s$ ) following

$$f_s = 1 / (2\pi \sqrt{LC}), \quad (4)$$

can be measured to determine the pH values (Figure 3b). To expand the sensing range and realize rapid detection to deep tissues, Liu et al. expanded the sensing range and developed hydrogel–metal systems, as Figure 3c illustrates, to detect anastomotic leakages after gastrointestinal surgeries [9]. They targeted gastric (pH~1), intestinal (pH = 6.8), and pancreatic

(pH > 7.4) leakage. The mechanism for pancreatic leakage detection is similar to the description above, relying on the carboxyl protonation of PAA. The crosslinking with hydrophobic butyl acrylate units hinders the protonation of carboxyl groups around the original pKa of the acrylic acid moieties and shifts the swelling transition to values larger than a pH of 7.4. On the other hand, since the leakage of gastric and the small intestine is more acidic, they employed poly [2-(dimethylamino)ethyl methacrylate-co-2-(diisopropylamino)ethyl methacrylate] ([p(DMAEMA-DPAEMA)]) with PEGDA. DMAEMA and DPAEMA contain tertiary amine moieties that undergo protonation and subsequent changes in osmotic pressure as the pH decreases. They embedded Zn disks between two layers of hydrogels with a thickness of 25  $\mu\text{m}$ . The sensors were small enough to be implanted with a size of 4 mm and thickness of 200  $\mu\text{m}$ . Other than X-ray, they selected ultrasound to characterize the length change of Zn disks since ultrasound can be bed-sided without damaging patients. They demonstrated successful pH-based leakage detection on all three target organs in both rodent and porcine models (Figure 3d), proving the ability of rapid leakage detection even in deep tissues up to the depth of 15 cm.



**Figure 3.** Representative examples for pH sensors: (a,b) Schematic illustration, photo and sensing results of the LC circuit-based bioresorbable, wireless, passive pH sensors. From ref. [146]. © The authors, some

rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license <http://creativecommons.org/licenses/by-nc/4.0/> (accessed on 25 June 2024). Reprinted with permission from AAAS. (c,d) Schematic illustration, photo and sensing results of the bioresorbable shape-adaptive pH sensors for ultrasonic monitoring of deep-tissue homeostasis. \*  $p < 0.05$ , \*\*  $p < 0.01$ . From ref. [9]. Reprinted with permission from AAAS. (e–h) Materials, schematic illustration, photo and sensing results of the wireless and flexible optoelectronic system for in situ monitoring of vaginal pH. Reprinted with permission from ref. [141]. Copyright 2023 Wiley-VCH.

Fluorescent properties can also be utilized as pH sensors. Gurkov et al. modified a pH-sensitive fluorescent dye, SNAFR-1, conjugated with dextran as a pH-sensitive probe (SNAFR-1-D) [147]. The probe can be trapped by semipermeable shells due to the conjugation of the dextran, forming microencapsulated biomarkers (MBMs). The excitation wavelength of SNAFR-1 is 560 nm, while the emission wavelengths are 587 nm and 627 nm. The sensitive dye shows the linear change in the ratio between the two peaks in pH 6 to 9. Thus, the pH can be determined by characterizing the intensity ratios at the peak of 587 nm and peak of 627 nm. As a proof-of-concept, they injected the MBMs into the pericardium of the zebrafish embryo, claiming the biocompatibility of such sensors without any effect on the embryo development, and moved along the smallest capillaries without disruption of the blood flow [148]. The sensors could detect the pH change successfully. Due to the size of MBMs, they are applicable to obtain signals from a single microcapsule with optical microscopy. Corsi et al. labeled poly-allylamine-hydrochloride (PAH) and poly-methacrylic-acid (PMAA) with a pH-sensitive fluorophore, Rhodamine-B (Rh), forming PAH:Rh and PMAA:Rh as positive and negative polyelectrolytes, respectively. These two functional layers were stacked onto a PLGA substrate after nanostructured porous silicon (nPSi) membrane assembly. The fluorescence showed a linear function of the pH value in the pH 4 to 7.5 due to the volume change of the polymer multilayers. The utilization of the nPSi reduced the toxicity and solubility of the fluorophores, therefore improving the functionality and biocompatibility [149]. Similarly, Paghi et al. assembled nPSi with pH-responsive fluorescent positive and negative polyelectrolyte stacks, as Figure 3e demonstrates [141]. They further integrated the pH sensors with miniaturized driving/readout optoelectronic circuits (light-emitting diode–photodetector pairs, LED–PD) and data acquisition systems encapsulated in polydimethylsiloxane (PDMS) rings to form the sensing vaginal rings, as Figure 3f,g show. The LED–PD realizes the excitation to the pH sensor and fluorescence emission collection. The photocurrent is then converted into a pH-dependent voltage signal and visualized to users (Figure 3h). The sensing vaginal rings can be placed inside the vagina and continuously work for up to 4 days. Such rings help to diagnose and manage bacterial vaginosis in females.

### 3.3. Temperature and Thermal Sensors

Most biological activities are performed under specific temperatures; this characteristic is also reflected in pathological changes, such as inflammation. Based on this feature, temperature measurement can be used to diagnose diseases such as traumatic brain injury, cardiovascular abnormalities, glaucoma, and neurogenic bladder dysfunction [144]. Although plenty of skin temperature sensors have been invented, they can only represent the inner body temperature indirectly and partially since normal body temperature does not mean a person is entirely healthy [150]. In situ temperature sensing provides more accurate and local temperature information, so implantable temperature sensors appeal to many interests. Moreover, temperature sensors are often integrated with other biomedical devices to realize more functions, such as controlled drug delivery. Shin J-W et al. designed a biodegradable electronic suture system with drug elution [33]. The suture consists of drug elution, heating threads, and a temperature sensor by W/Mg. The temperature monitoring ensures controlled drug delivery without extra injury due to overheating.

Several mechanisms are employed to design temperature sensors. One commonly used mechanism is utilizing the thermal effect on the electrical resistance. The resistance of sensing materials shows a relationship with temperature as follows:

$$R = R_0(1 + \alpha(T - T_0)), \quad (5)$$

where  $R$  is the resistance at temperature  $T$ ,  $R_0$  is the initial resistance at temperature  $T_0$ , and  $\alpha$  is the temperature coefficient of resistance (TCR) [20]. Recently, Zhao et al. deployed germanium nanomembranes as the active materials, shown in Figure 4a,b, because of the elimination of gaseous products, small forbidden bandwidth, and large carrier mobility [20]. Germanium nanomembranes were transferred and adhered onto spin-on-glass layers and assembled with metal bottom substrates, SiO<sub>2</sub> insulator layers, Au nanomembrane electrodes, and SiO<sub>2</sub> top encapsulation layers. The temperature sensor performed a high TCR of  $2.4 \times 10^{-3}$ , a desired sensitivity of  $105 \Omega/^\circ\text{C}$ , and a good resolution of  $0.1^\circ\text{C}$  (Figure 4c). The TCR can be enhanced by doping since germanium is a semiconductor. The inductor–capacitor (LC)-based mechanism could also be applied if the materials show temperature-sensitive properties. For example, Lu et al. deployed polyethylene glycol (PEG) as the sensor unit since the dielectric constant ( $\epsilon_r$ ) shows a strong temperature dependence near body temperatures [151]. By integrating with the Mg inductor, the temperature sensor could monitor the body temperature with desired precision, accuracy, and drift performance.

Optical-based temperature sensors were also extensively developed using Fabry–Pérot (FP) cavity structures. The resonant peak wavelength ( $\lambda_q$ ) of the  $q^{\text{th}}$  order of an FP cavity is

$$\lambda_q = \frac{2nt}{q}, \quad (6)$$

where  $n$  is the refractive index, and  $t$  is the thickness of the cavity. TCR can be expressed as

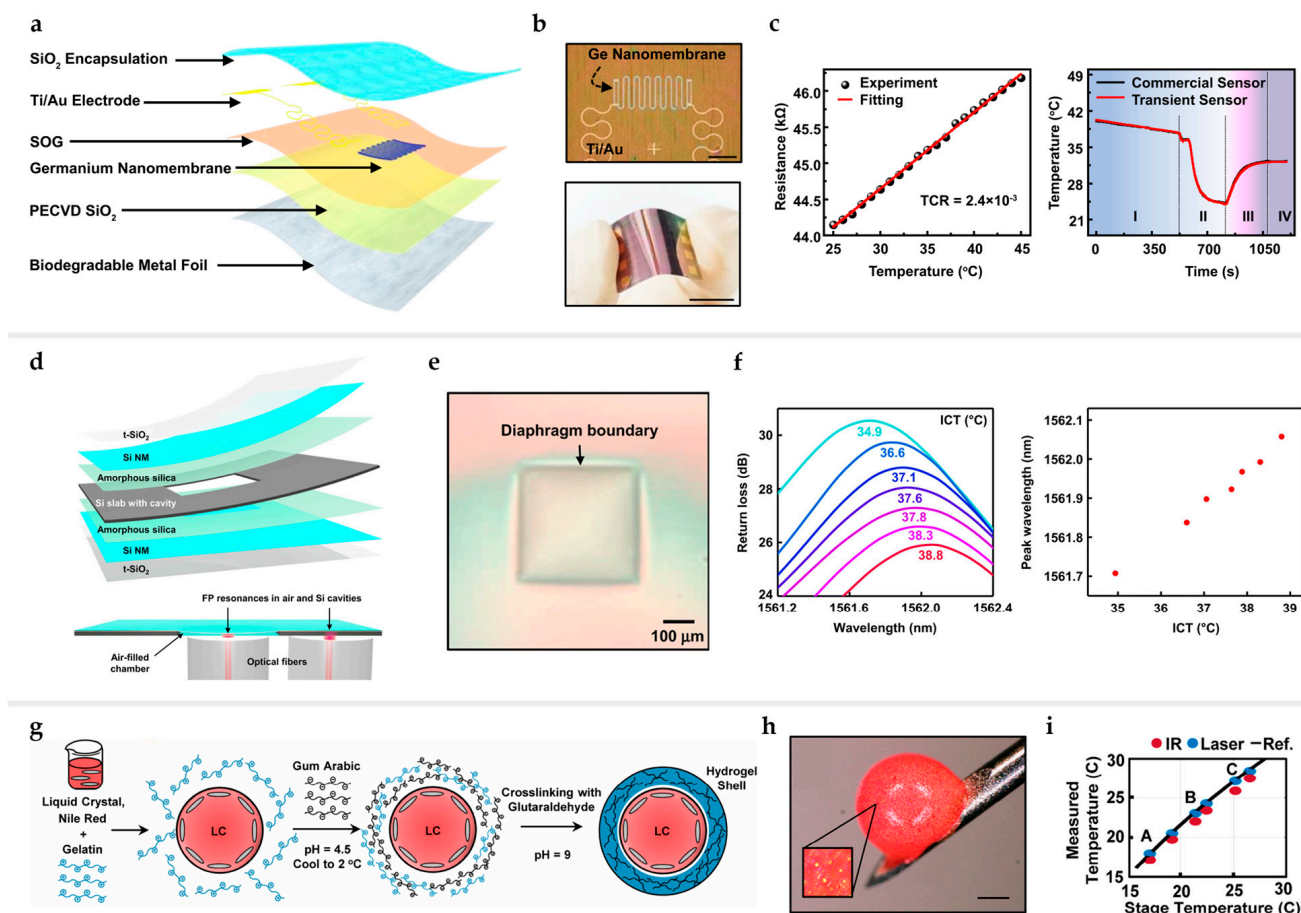
$$\alpha = \frac{1}{t} \frac{dt}{dT}, \quad (7)$$

By differentiating Equation (6) and combining it with Equation (7), the relationship can be determined as follows [152]:

$$\frac{d}{dT} \lambda_q = \frac{2t}{q} \left( \frac{dn}{dT} + \alpha n \right) \quad (8)$$

If the second component can be neglected, then the resonant wavelength shift with temperature positively correlates to the thermo-optical coefficient. Shin J. et al. designed a Fabry–Pérot interferometer (FPI) sensor for temperature and temperature sensing, as Figure 4d,e show [153]. The components of the FPI sensor include top and bottom thermally grown SiO<sub>2</sub>, a Si NM, an amorphous SiO<sub>2</sub> adhesion layer, and a Si slab. Focused on temperature sensing, the increase in temperature redshifts the FP resonance peaks since the Si-based NM has a positive thermo-optic coefficient. The temperature sensor has a responsivity of  $0.090 \text{ nm}/^\circ\text{C}$ , and the sensing range is between  $27^\circ\text{C}$  and  $46^\circ\text{C}$  with an accuracy of  $\pm 0.12^\circ\text{C}$  (Figure 4f). Bai et al. also used Si-related NMs to fabricate implantable temperature sensors. Here, they stacked SiO<sub>2</sub> and SiN<sub>x</sub> layers and assembled the stack with a Si layer on a PLGA substrate to form a multilayer reflective photonic cavity structure. The SiO<sub>2</sub> and SiN<sub>x</sub> layers serve as a distributed Bragg reflector (DBR) defect cavity, while the Si layer serves as an FP cavity. The exploitation of the DBR and FP cavities eliminates the problem resulting from the incident light angles. From the refractive spectra, one peak can determine the incident angle under DBR defect mode, and another peak can determine the temperature under an adjacent FP mode. Implanting such a temperature sensor into the rodent model, their devices detected the temperature of awake mice with a measurement accuracy of  $0.2^\circ\text{C}$  and a precision of  $0.1^\circ\text{C}$ . Franklin et al. fabricated a CLC microdroplet

(Figure 4g,h) [105]. Temperature influences the pitch of the CLC molecular helix a lot due to intermolecular distance and order. Thus, the resonant wavelength of the cavity determined by intermolecular distance and order can represent the temperature change. The CLC is biodegradable since it mainly consists of cholesteryl ester. The components of CLC determine the sensitivity of the sensors, which ranges from  $-300$  to  $4 \text{ nm}/^{\circ}\text{C}$  (Figure 4i).



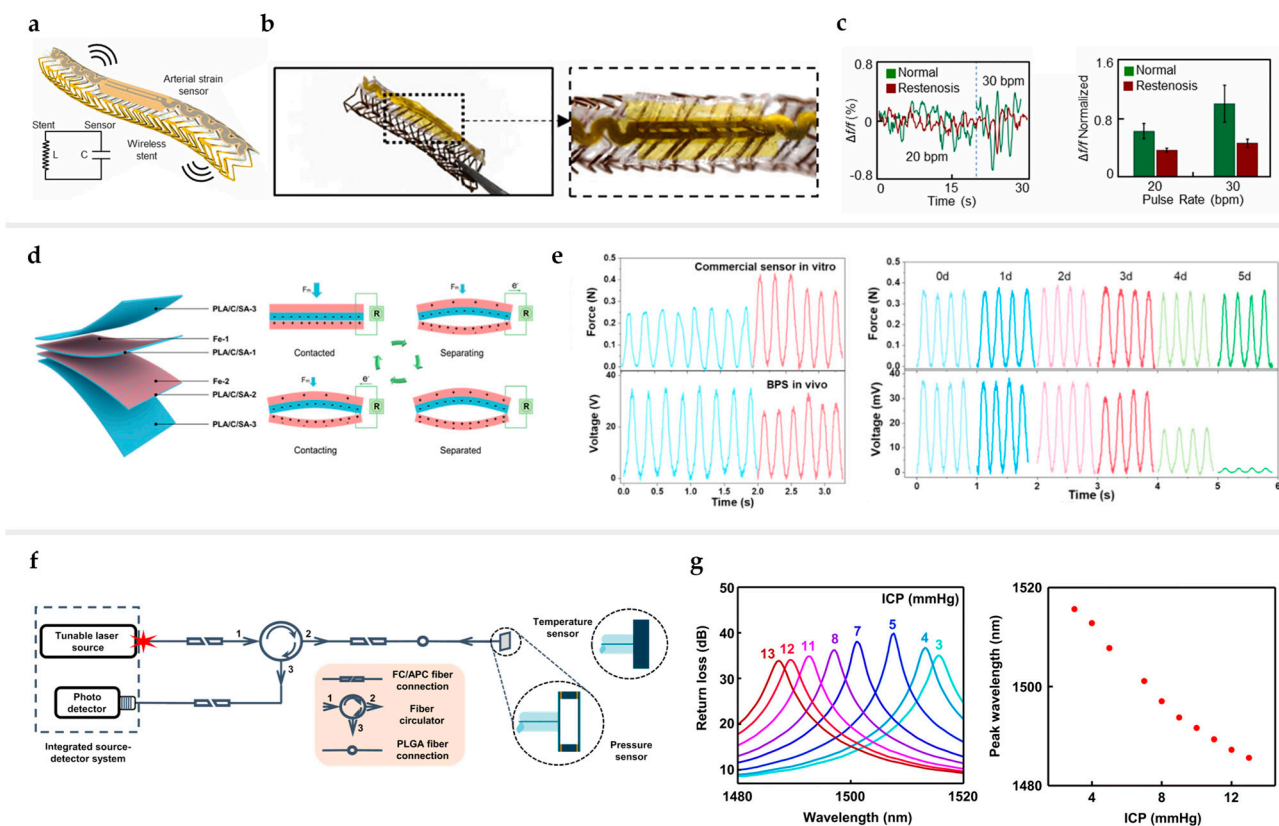
**Figure 4.** Representative examples for temperature sensors: (a–c) Schematic illustration, photo and sensing results of the thermal effect-based temperature sensors made of biodegradable germanium. Reprinted with permission from ref. [20]. Copyright 2022 Springer Nature. (d–f) Schematic illustration, photo and sensing results of optical FPI temperature sensors. From ref. [153]. © The authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license <http://creativecommons.org/licenses/by-nc/4.0/> (accessed on 25 June 2024). Reprinted with permission from AAAS. (g–i) Schematic illustration, photo and sensing results of the bioresorbable microdroplet lasers for transient thermal sensing and modulation Reprinted with permission from ref. [105]. Copyright 2021 American Chemical Society.

### 3.4. Pressure and Strain Sensors

Mechanical sensors are crucial in providing information to diagnose a range of conditions, from normal to life-threatening. For example, they can help avoid bone growth hindrance after implanting bone fixation plates [113], identify vascular occlusion events [154], and monitor tumor progress [155,156].

Various strategies have been developed to design mechanical sensors such as pressure and strain sensors. One reliable strategy for creating passive resonance sensors is LC circuits. As shown in Equation (4), changes in capacitance ( $C$ ) can shift the resonance frequency. Resonance pressure sensors generally use two deformable, conductive membranes as parallel plate capacitors, where the distance between the plates affects capacitance. Thus, as the pressure increases, the distance between the plates reduces, resulting in detectable

resonance frequency shifting. A recent study by Palmroth et al. demonstrated the design of a pressure sensor based on LC circuits using bioactive-glass-based materials and encapsulation films with atomic layer deposition [113]. The use of bioactive glass allows strong bonding interfaces between implants and bones, release of soluble ions, and stimulation of osteogenic cells to promote bone growth. The sensors were fabricated with S53P4 glass substrates, biodegradable metal conductors, and spin-coated poly(desaminotyrosyl-tyrosine ethyl ester carbonate) (PDTEC) dielectric layers. Using different metals, the sensitivity range was realized between  $-5.1$  and  $-9.4$  kHz/mmHg, with a maximum detecting distance of up to 15 mm. Herbert et al. applied the same mechanism to fabricate strain sensors by placing Ag NPS onto polyimide substrates using the AJP approach [16]. These flexible strain sensors were used to detect the stiffness of cardiac tissue, facilitating the diagnosis of atherosclerosis (Figure 5a,b). The strain sensors showed a wide sensing range larger than 2 to 5%, which is the maximum expected artery wall strain, and the sensitivity was high at over 1.5.



**Figure 5.** Representative examples for mechanical sensors: (a–c) Schematic illustration, photo and sensing results of the LC circuit-based mechanical sensors for arterial stiffness. Reprinted with permission from ref. [16]. Copyright 2022 Elsevier. (d,e) Schematic illustration and sensing results of the triboelectric-based bioresorbable pressure sensor and for abnormal respiratory event identification. Reprinted with permission from ref. [157]. Copyright 2023 American Chemical Society. (f,g) Schematic illustration, and sensing results of the optical FPI temperature sensors. From ref. [153]. © The authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license <http://creativecommons.org/licenses/by-nc/4.0/> (accessed on 25 June 2024). Reprinted with permission from AAAS.

Biodegradable triboelectric sensors (BTSs) and piezoelectric sensors (BPSs) were also developed since they convert pressure into electrical signals. Triboelectric materials produce charge transfer with friction forces. Thus, some BTSs contain cavities between two triboelectric layers. As pressure increases, the two layers contact and rub with each other,

generating charge transfer and, thereby, output of electric signals. The pressure change ( $\Delta P$ ) can be calculated by

$$\Delta P = \frac{nRT\varepsilon_0}{x_0\sigma} U_{oc}, \quad (9)$$

where  $n$  represents the number of moles,  $R$  represents the universal gas constant,  $T$  represents the temperature,  $\varepsilon_0$  represents the permittivity of the vacuum,  $x_0$  represents the initial displacement,  $\sigma$  represents surface charge density, and  $U_{oc}$  represents the open-circuit voltage [154]. For instance, Ouyang et al. paired poly(lactic acid)–(chitosan 4%) (PLA/C) and Mg as the triboelectric layers [152]. After contacting and rubbing, the electrons on the Mg surface transfer to the PLA/C surface and output the open circuit voltage. They successfully applied the sensors to both the small animal model detecting dyspnea events and the large model detecting arrhythmia events and monitoring blood pressure. The sensor shows desired properties with a service efficiency of 6%, sensitivity of 11 mV/mmHg, and durability of 450,000 cycles. Similarly, Li Z. et al. modified PLA/C with sodium alginate (PLA/C/SA) to improve the roughness due to the hemispherical micro–nano structure [157]. Fe and PLA/C/SA were used as triboelectric layers (Figure 5d). The sensor improved its sensitivity to 22.61 mV/mmHg and its durability to 850,000 cycles. They tested the pressure sensors with the small animal model and detected abnormal respiratory events (Figure 5e). Apart from triboelectric materials, piezoelectric materials also convert mechanical properties to electrical signals. Chielsa et al. employed silk as the piezoelectric material, modified with graphene/tannin to improve the electrical, mechanical, and adhesive properties [48]. Adhering to the intestine, voltages can be measured to detect gastrointestinal motility for up to 21 days.

Some materials show resistance changes sensitive to the strain, which is another mechanism for mechanical sensors. The gauge factor ( $GF$ ) can be determined by

$$GF = \frac{\Delta R/R}{\Delta L/L} = \frac{\Delta R/R}{\varepsilon} = 1 + 2\nu + \frac{\Delta\rho/\rho}{\varepsilon} \quad (10)$$

Here,  $\Delta R$  is the change in strain resistance,  $R$  is the unstrained resistance,  $\Delta L$  is the change in length,  $L$  is the original length,  $\nu$  is the Poisson's ratio,  $\rho$  is the resistivity, and  $\varepsilon$  is the strain [158]. As the equation shows,  $GF$  shows inversely proportional relationships to the strain and thereby converts strain into electrical signals. Qiao et al. synthesized a gelatin/polyacrylamide double-network hydrogel doped with  $Mg^{2+}$  and  $Ca^{2+}$  ions [158]. The hydrogel withstands strains up to 5000% before failure with a tensile strength of 1.71 MPa and shows sensitive changes in the resistivity due to the deformation of the hydrogel. The  $GF$  changes from 1.63 to 6.85 for the strains of 100% to 2100% with 20 mM of  $Ca^{2+}$  doping. Kang et al. synthesized another double-network hydrogel of PVA/PAA, filled by CNT nanofillers with the  $GF$  of 1.12 [159]. The nanofillers adjust the hydrogel moduli to match the target soft tissue, with a conductivity of 20 S/m, a stretchability of 1000% strain, and a toughness of 400 to 731 kJ/m<sup>3</sup>. The germanium nanomembranes developed by Zhao et al. also show a similar ability to detect strain change with an estimated  $GF$  of 27 [20]. Such sensors can simultaneously measure the temperature and strain after calibration.

Mechanical sensors can be used for monitoring purposes in addition to temperature sensors, and thereby can serve other functions such as drug delivery. For example, Kaveti et al. developed an electronic surgical mesh that has pressure-monitoring capabilities along with on-demand drug delivery [52]. The system consists of two components: (i) a pressure-monitoring unit made of asymmetric Mg double-coils and a ZnO/PLCL dielectric layer, and (ii) a drug delivery system consisting of a Mg inductive coil, a Mg microheater, and a Mg/SiO<sub>2</sub>/Mg capacitor. The pressure sensors have a sensitivity of 1.2 kPa<sup>−1</sup>, and the drug delivery system can release 88% of the drug within 3 days, driven under 42 °C. The mesh was implanted into rats with an abdominal hernia repair model, and pressure monitoring was performed for up to 15 days. The on-demand drug delivery was demonstrated to enhance the healing process and improve inflammation and fibrosis degrees at the early stage.

### 3.5. Sensors for Nervous System Diagnosis

The nervous system plays roles in nearly all aspects of health and daily life. The system controls essential vital activities such as breathing, heartbeats, and body temperature; it receives external sensations and guides movements; it performs advanced and complex processes such as thinking and feeling emotions [160]. Diseases of the nervous system, such as Alzheimer's disease, Parkinson's disease, epilepsy, and mental illnesses, including major depression, eating disorder, and anxiety, are still open fields requiring more studies to understand the mechanism behind them. Precise sensors to monitor nervous system indexes and neuron activities are crucial to help diagnose and track health and wellbeing status. In recent decades, sensors focusing on different signals, including physical, chemical, and electrical, have made much progress. Some sensors can even realize multiple functions simultaneously. In this section, a brief review of different types of sensors for the nervous system is provided to inspire the sensors for complex systems.

The brain is protected by the skull and related biofluids, such as cerebrospinal fluid. As liquid, the biofluids produce pressure inside the skull, named intracranial pressure (ICP). It is essential to keep a stable ICP. Increased ICP will cause life-threatening conditions. Thus, monitoring after brain trauma is necessary. Shin J. et al. further developed FPI-based pressure sensors in addition to the temperature sensors, as Figure 5f shows [153]. As Equation (5) demonstrates, changes in the thickness of the FP cavity will shift the resonant peak wavelength (Figure 5g). Therefore, they left a cavity between the two layers of Si NM. With the ability to detect temperature changes introduced above, their devices could monitor the ICP by eliminating temperature influence. The FPI sensors have the advantage, compared with another design, photonic crystal sensors, that the changes in resonance peaks rely on photonic crystal lattice constant change (strain) and Maxwell's equations and electromagnetic wave theory (temperature). The reflection spectrum of FPI sensors is independent of light incidence angle, intensity, and position of the beam, eliminating the noise due to the natural body movement and biofluid coating. Moreover, Lu et al. designed LC-based pressure sensors with Mg, Zn, SiN, and PLGA [161], while Shin J. et al. designed GF-based pressure sensors with Si due to its piezoelectric property [162]. Both types of sensors showed acute and efficient measurement of ICP.

Sensors mainly aimed at monitoring neural activities were also developed. Wu et al. successfully detected the dopamine and glutamate concentration by CNT/PtNP/Nafion and CNT/PtNP/Nafion/Glutamate oxidase (GluOx) fibers, respectively [163]. Fibers served as the gate electrode, accompanied by PEDOT:PSS channel and chromium/Au drain and source electrodes. Because of the electrochemical reactions, the concentration of associated chemicals could be transduced into electrical signals, similar to other electrochemical-based chemical sensors. Optical sensors could also detect neural activities. Biodegradable photonic devices developed by Bai et al. incorporated PLGA biodegradable optical fibers with different optical components to realize different sensing functions [6]. Among the optical components, the  $\text{SiO}_x/\text{SiN}_y$  stacking filter effectively blocks excitation light and transmits emission light for a  $\text{Ca}^{2+}$ -sensitive fluorophore, providing the potential to detect the Ca transients in neural tissues. Assembled with a PLGA optical fiber, a  $\text{SiO}_x/\text{SiN}_y$  stacking optical filter, and a Si NM photodetector, the device output the photocurrent after being implanted into the parietal lobe of a mouse, stained with small-molecule Ca fluorescent dyes.

Brain waves could also represent neural activities at a macro level. Yu et al. fabricated a biodegradable electrode array to realize the recording of the ECoG, which is the electrical potential associated with brain activity from the cerebral cortex [107]. The ECoG of ionic currents in the electrolyte can be transduced into an electric current and measured by the recording electrodes. They designed 4-channel passive recording electrodes with active materials (Si NM) and dielectric/insulation layers ( $\text{SiO}_2$ ) to capture acute and chronic ECoG waves. They also designed 64-channel actively multiplexed devices with Mo electrodes,  $\text{SiO}_2$  gate dielectric, and  $\text{SiO}_2/\text{SiN}/\text{SiO}_2$  dielectric layers to realize the mapping of ECoG signals. To demonstrate concepts, acute ECoG from rats with epileptiform activity and

whisker stimulation and chronic ECoG from healthy rats were recorded successfully with minimal immune response. Similarly, Xu K. et al. designed a 6-channel ECoG recording system with Mo and PLA: PCL encapsulations [164]. Their devices captured dynamic changes in brain signals at different epilepsy stages. Meanwhile, due to the PLA:PCL malleability, the sensors' resistance showed a linear relationship with pressure, as demonstrated at GF-based pressure sensors. The swelling of the cortex due to surgery could be detected, as claimed. Xie J. et al. modified Pt NP with GluOx for electrical signals and recording glutamate detection [165]. By integrating with graphene oxide (GO) as the adhesion between Pt NP and GluOx and 1,3-phenylenediamine (mPD) as the anti-interference of another chemical in the brain, they developed PtNPs/rGO-GluOx/mPD microelectrodes. This electrode array could record the electric signals from the cortex and hippocampus and sense the concentration of glutamate, giving a better understanding of epilepsy mechanisms.

#### 4. Challenge and Prospects

In this review, we provided a brief overview of the materials and recent fabrication approaches used for biosensors. We also discussed recent developments in implantable and semi-implantable biosensors, which are focused on a variety of health and wellbeing aspects. The use of advanced biodegradable and nanomaterials helps to reduce injury due to secondary removal surgeries, and the capability to adjust properties allows customers to design devices based on their specific requirements. Novel fabrication techniques provide support to produce devices with efficiency, precision, and reasonable costs.

Despite the advantages of the recent biosensors, some challenges should be addressed. The first limitation is the biosafety and biocompatibility of materials. It was proved that most of the products from biodegradable materials are biocompatible, and the accumulation of elements should be considered. With degradation, the performance of devices can decrease, so the thickness of the devices should be sufficient to perform designed functions [166]. However, although proven biocompatible, the element accumulation should not exceed recommended daily intake values (~tens of  $\mu\text{g}$  to hundreds of  $\text{mg}$  per day) depending on elements [167,168], especially W, which is not a universal bioelement. Thus, the selection of materials for biosensing devices should consider the working lifetime, targeted biological environment, and designed thickness to maintain the functions during the working timeframe without over-limited accumulation of elements in the human body. On the other hand, the biosafety of nanomaterials still needs more study and characterization. As stated above, the large surface area and the tailing ability make nanomaterials ideal functional materials for biosensing; such material can also trigger special biological effects with biomolecules and cells, bringing potential adverse influence on human health [169]. Some studies indicate that nanoparticles, such as small Au NPs, can be directly phagocytosed by phagocytes [100]. However, the interactions between cells and some other nanomaterials are still left some blank, and the ability to remove non-resorbable nanomaterials is a problem to be solved, as mentioned above. Mechanical matching with tissues is another aspect that needs to be improved. For example, the brain tissue is one of the softest tissues in the human body ( $<10\text{ kPa}$ ) [7], but probes for deep tissues are usually much stiffer, which may lead to irreversible injury to the brain.

Another challenge to consider occurs during implantation. For example, when implanting a large scale of micro- and nanoelectrode arrays, it is difficult to ensure precise localization and minimal injury simultaneously. Sigurdsson et al. created a PEG microneedle array that can load small sizes of nanodevices [170]. After the degradation of PEG, the devices could remain in their original position without influencing the functions. However, they also demonstrated a lack of quantification of chronic migration. The adhesion between devices and wet tissues is usually weak, which hinders accuracy and efficiency. Adhesions developed by Yuk et al. [171], Yang et al. [82], etc., aimed to use adhesive hydrogels to realize device adhesion, but the ability to maintain chronic adhesion for up to years should be improved for chronic biomedical devices.

Moreover, integrating different functions in one device can be studied further. As per the introductions in the Section 3, most devices only realize several functions, as the factors may interfere. Some devices show the potential to sense various factors, such as pressure, temperature, flow, thermal diffusivity, pH, and chemical sensing together [172]; the accuracy of each measurement needs to be studied and proved. Some devices integrate biosensors with therapeutic systems such as drug delivery. However, only a few of them utilize biosensors as the control unit to realize the close-loop therapy, avoiding over- or under-treatment.

Some biosensors transmit and store the data locally throughout the readout equipment [9,146], and some biosensors utilize wireless data transmit system such as Bluetooth [4,141]. Some biosensors rely on self-designed smartphone applications using App tools [3]. In this case, the security of data transfer should be considered seriously, since it is related to the privacy of patients. Bluetooth communication, as an example, uses long term keys, connection signature resolving keys and identity resolving keys during pairing process [173]. But some hardware makes it possible to read and decode Bluetooth communication [174]. Some methodologies were developed, such as watchdog record [175], machine learning intrusion detection systems [176], and so on. Advanced methodologies to protect data security need to be further developed by software and hardware engineering.

In general, in order to achieve the potential benefits, it is necessary to have effective collaboration between material science and engineering, electrical engineering, and biological science and engineering. With the development of related science and engineering, it is possible to achieve multifunctional implantable and semi-implantable biomedical sensors to obtain various critical information in real time for disease diagnosis and health monitoring, therefore improving the efficacy and accuracy of clinical activities and convenience to patients. By combining multifunctional biosensing and therapeutic systems, we can also implement close-loop control of therapy and modulation to avoid over- or under-treatment to individual patients. The data can be transferred by modern technology such as Bluetooth and specific smartphone applications, and, thereafter, make contributions to big data for medical development.

**Author Contributions:** Conceptualization, Y.X., W.Z.R. and M.R.M.; writing—original draft preparation, Y.X. and J.Z.; writing—review and editing, Y.X., J.Z., W.Z.R. and M.R.M.; visualization, Y.X. and J.Z.; supervision, W.Z.R. and M.R.M.; project administration, W.Z.R. and M.R.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Acknowledgments:** We acknowledge the advice and support from Ying Yan, department of neurosurgery, Washington University School of Medicine in St. Louis.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

| Abbreviation | Full name                                            |
|--------------|------------------------------------------------------|
| Ag           | silver                                               |
| AJP          | aerosol jet printing                                 |
| Au           | gold                                                 |
| BGF          | biodegradable glucose-responsive fluorescent monomer |
| BPS          | biodegradable piezoelectric sensors                  |
| BTS          | biodegradable triboelectric sensors                  |
| Ca           | calcium                                              |
| CE           | counter electrodes                                   |
| CLC          | cholesteric liquid crystal                           |
| CT           | computed tomography                                  |

|                               |                                                         |
|-------------------------------|---------------------------------------------------------|
| DBR                           | distributed Bragg reflector                             |
| DMAEMA                        | 2-(dimethylamino)ethyl methacrylate                     |
| DPAEMA                        | 2-(diisopropylamino)ethyl methacrylate                  |
| ECoG                          | electrocorticogram                                      |
| FPI                           | Fabry–Pérot interferometer                              |
| GelMA                         | gelatin methacrylate                                    |
| GF                            | gauge factor                                            |
| GluOx                         | glutamate oxidase                                       |
| GO                            | graphene oxide                                          |
| GOx                           | glucose oxidase                                         |
| H <sub>2</sub> O <sub>2</sub> | hydrogen peroxide                                       |
| Hb                            | deoxyhemoglobin                                         |
| HbO <sub>2</sub>              | oxyhemoglobin                                           |
| HEDN                          | highly entangled double network                         |
| HPU                           | hydrophilic polyurethanes                               |
| ICP                           | intracranial pressure                                   |
| IrO <sub>2</sub>              | iridium(IV) oxide                                       |
| LED                           | light-emitting diode                                    |
| MBM                           | microencapsulated biomarkers                            |
| Mg                            | magnesium                                               |
| Mo                            | molybdenum                                              |
| MRI                           | magnetic resonance imaging                              |
| mPD                           | 1,3-phenylenediamine                                    |
| m-Si                          | monocrystalline silicon                                 |
| MWCNT                         | multiwalled carbon nanotube                             |
| NM                            | nanomembrane                                            |
| NP                            | nanoparticle                                            |
| nPSi                          | nanosstructured porous silicon                          |
| NR                            | nanorod                                                 |
| NT                            | nanotube                                                |
| OE                            | organic electrodes                                      |
| OECT                          | organic electrochemical transistors                     |
| PA                            | phytic acid                                             |
| PAA                           | polyacrylic acid                                        |
| PAH                           | poly-allylamine-hydrochloride                           |
| PANI                          | polyaniline                                             |
| PCL                           | poly( $\epsilon$ -caprolactone)                         |
| PD                            | photodetector                                           |
| PdBMAP                        | Pd (II) tetramethacrylated benzoporphyrin               |
| PDMS                          | polydimethylsiloxane                                    |
| PDO                           | polydioxanone                                           |
| PDTEC                         | poly(desaminotyrosyl-tyrosine ethyl ester carbonate)    |
| PEDOT:PSS                     | poly(3,4-ethylene dioxythiophene) polystyrene sulfonate |
| PEG                           | polyethylene glycol                                     |
| PEGDA                         | poly(ethylene glycol)diacrylate                         |
| PEG-LA-DA                     | polyethylene glycol-lactide acid diacrylate             |
| PGA                           | polyglycolide                                           |
| PGCL                          | poly(glycolide-co- $\epsilon$ -caprolactone)            |
| PGS                           | poly(glycerol-co-sebacate)                              |
| PLA                           | poly(lactic acid)                                       |
| PLGA                          | poly lactic-co-glycolic acid                            |
| PLLA                          | poly-L-lactic acid                                      |
| PMAA                          | poly-methacrylic-acid                                   |
| PPMM                          | polypropylene micromembrane                             |
| Pt                            | platinum                                                |
| PVA                           | polyvinyl alcohol                                       |
| QD                            | quantum dot                                             |
| RE                            | reference electrodes                                    |

|                  |                                       |
|------------------|---------------------------------------|
| Rh               | Rhodamine-B                           |
| SA               | sodium alginate                       |
| Si               | silicon                               |
| SPCE             | screen-printed carbon electrodes      |
| SPRi             | surface plasmon resonance image       |
| StO <sub>2</sub> | oxygen saturation                     |
| TCR              | temperature coefficient of resistance |
| VEGF             | vascular endothelial growth factor    |
| W                | tungsten                              |
| WHO              | World Health Organization             |
| Zn               | zinc                                  |

## References

1. Ayres, J.S. The Biology of Physiological Health. *Cell* **2020**, *181*, 250–269. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Wang, H.-C.; Lee, A.-R. Recent developments in blood glucose sensors. *J. Food Drug Anal.* **2015**, *23*, 191–200. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Sang, M.; Cho, M.; Lim, S.; Min, I.S.; Han, Y.; Lee, C.; Shin, J.; Yoon, K.; Yeo, W.-H.; Lee, T.; et al. Fluorescent-based biodegradable microneedle sensor array for tether-free continuous glucose monitoring with smartphone application. *Sci. Adv.* **2023**, *9*, eadh1765. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Li, J.; Liu, J.; Wu, Z.; Shang, X.; Li, Y.; Huo, W.; Huang, X. Fully printed and self-compensated bioresorbable electrochemical devices based on galvanic coupling for continuous glucose monitoring. *Sci. Adv.* **2023**, *9*, eadi3839. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Guo, H.; Bai, W.; Ouyang, W.; Liu, Y.; Wu, C.; Xu, Y.; Weng, Y.; Zang, H.; Liu, Y.; Jacobson, L.; et al. Wireless implantable optical probe for continuous monitoring of oxygen saturation in flaps and organ grafts. *Nat. Commun.* **2022**, *13*, 3009. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Bai, W.; Shin, J.; Fu, R.; Kandela, I.; Lu, D.; Ni, X.; Park, Y.; Liu, Z.; Hang, T.; Wu, D.; et al. Bioresorbable photonic devices for the spectroscopic characterization of physiological status and neural activity. *Nat. Biomed. Eng.* **2019**, *3*, 644–654. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Budday, S.; Ovaert, T.C.; Holzapfel, G.A.; Steinmann, P.; Kuhl, E. Fifty Shades of Brain: A Review on the Mechanical Testing and Modeling of Brain Tissue. *Arch. Comput. Methods Eng.* **2020**, *27*, 1187–1230. [\[CrossRef\]](#)
8. Hunt, K.D.; O’Loughlin, V.D.; Fitting, D.W.; Adler, L. Ultrasonic determination of the elastic modulus of human cortical bone. *Med. Biol. Eng. Comput.* **1998**, *36*, 51–56. [\[CrossRef\]](#)
9. Liu, J.; Liu, N.; Xu, Y.; Wu, M.; Zhang, H.; Wang, Y.; Yan, Y.; Hill, A.; Song, R.; Xu, Z.; et al. Bioresorbable shape-adaptive structures for ultrasonic monitoring of deep-tissue homeostasis. *Science* **2024**, *383*, 1096–1103. [\[CrossRef\]](#)
10. Hormuzdi, S.G.; Filippov, M.A.; Mitropoulou, G.; Monyer, H.; Bruzzone, R. Electrical synapses: A dynamic signaling system that shapes the activity of neuronal networks. *Biochim. Biophys. Acta* **2004**, *1662*, 113–137. [\[CrossRef\]](#)
11. Kandel, E.R.; Schwartz, J.H.; Jessell, T.M. *Principles of Neural Science*; McGraw-Hill Professional: New York, NY, USA, 2000.
12. Feiner, R.; Dvir, T. Tissue–electronics interfaces: From implantable devices to engineered tissues. *Nat. Rev. Mater.* **2017**, *3*, 17076. [\[CrossRef\]](#)
13. Mistral, J.; Ve Koon, K.T.; Fernando Cotica, L.; Sanguino Dias, G.; Aparecido Santos, I.; Alcouffe, P.; Milhau, N.; Pin, D.; Chapet, O.; Serghei, A.; et al. Chitosan-Coated Superparamagnetic Fe<sub>3</sub>O<sub>4</sub> Nanoparticles for Magnetic Resonance Imaging, Magnetic Hyperthermia, and Drug Delivery. *ACS Appl. Nano Mater.* **2024**, *7*, 7097–7110. [\[CrossRef\]](#)
14. Handali, P.R.; Webb, L.J. Quantifying Bound Proteins on Pegylated Gold Nanoparticles Using Infrared Spectroscopy. *ACS Appl. Bio Mater.* **2024**, *7*, 2338–2345. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Mamidi, N.; Delgadillo, R.M.V.; González-Ortiz, A. Engineering of carbon nano-onion bioconjugates for biomedical applications. *Mater. Sci. Eng. C-Mater. Biol. Appl.* **2021**, *120*, 11. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Herbert, R.; Elsisy, M.; Rigo, B.; Lim, H.-R.; Kim, H.; Choi, C.; Kim, S.; Ye, S.-H.; Wagner, W.R.; Chun, Y.; et al. Fully implantable batteryless soft platforms with printed nanomaterial-based arterial stiffness sensors for wireless continuous monitoring of restenosis in real time. *Nano Today* **2022**, *46*, 101557. [\[CrossRef\]](#) [\[PubMed\]](#)
17. O’Brien, D.J.; Mills, D.; Farina, J.; Paranjape, M. A Needle-Free Transdermal Patch for Sampling Interstitial Fluid. *IEEE Trans. Biomed. Eng.* **2023**, *70*, 2573–2580. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Li, J.W.; Schartner, E.; Musolino, S.; Quirk, B.C.; Kirk, R.W.; Eboroff-Heidepriem, H.; McLaughlin, R.A. Miniaturized single-fiber-based needle probe for combined imaging and sensing in deep tissue. *Opt. Lett.* **2018**, *43*, 1682–1685. [\[CrossRef\]](#)
19. Hu, C.; Wang, L.; Liu, S.; Sheng, X.; Yin, L. Recent Development of Implantable Chemical Sensors Utilizing Flexible and Biodegradable Materials for Biomedical Applications. *ACS Nano* **2024**, *18*, 3969–3995. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Zhao, H.; Xue, Z.; Wu, X.; Wei, Z.; Guo, Q.; Xu, M.; Qu, C.; You, C.; Mei, Y.; Zhang, M.; et al. Biodegradable germanium electronics for integrated biosensing of physiological signals. *npj Flex. Electron.* **2022**, *6*, 63. [\[CrossRef\]](#)
21. Ryu, H.; Seo, M.-H.; Rogers, J.A. Bioresorbable Metals for Biomedical Applications: From Mechanical Components to Electronic Devices. *Adv. Healthc. Mater.* **2021**, *10*, 2002236. [\[CrossRef\]](#)
22. Kang, S.-K.; Koo, J.; Lee, Y.K.; Rogers, J.A. Advanced Materials and Devices for Bioresorbable Electronics. *Acc. Chem. Res.* **2018**, *51*, 988–998. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Yin, L.; Cheng, H.; Mao, S.; Haasch, R.; Liu, Y.; Xie, X.; Hwang, S.-W.; Jain, H.; Kang, S.-K.; Su, Y.; et al. Dissolvable Metals for Transient Electronics. *Adv. Funct. Mater.* **2014**, *24*, 645–658. [\[CrossRef\]](#)

24. Kang, S.-K.; Park, G.; Kim, K.; Hwang, S.-W.; Cheng, H.; Shin, J.; Chung, S.; Kim, M.; Yin, L.; Lee, J.C.; et al. Dissolution Chemistry and Biocompatibility of Silicon- and Germanium-Based Semiconductors for Transient Electronics. *ACS Appl. Mater. Interfaces* **2015**, *7*, 9297–9305. [[CrossRef](#)] [[PubMed](#)]
25. Zheng, Y.F.; Gu, X.N.; Witte, F. Biodegradable metals. *Mater. Sci. Eng. R Rep.* **2014**, *77*, 1–34. [[CrossRef](#)]
26. Choi, Y.; Koo, J.; Rogers, J.A. Inorganic materials for transient electronics in biomedical applications. *MRS Bull.* **2020**, *45*, 103–112. [[CrossRef](#)]
27. Hosseini, E.S.; Dervin, S.; Ganguly, P.; Dahiya, R. Biodegradable Materials for Sustainable Health Monitoring Devices. *ACS Appl. Bio Mater.* **2021**, *4*, 163–194. [[CrossRef](#)] [[PubMed](#)]
28. Huang, X.; Wang, D.; Yuan, Z.; Xie, W.; Wu, Y.; Li, R.; Zhao, Y.; Luo, D.; Cen, L.; Chen, B.; et al. A Fully Biodegradable Battery for Self-Powered Transient Implants. *Small* **2018**, *14*, 1800994. [[CrossRef](#)]
29. Kim, H.-S.; Yang, S.M.; Jang, T.-M.; Oh, N.; Kim, H.-S.; Hwang, S.-W. Bioresorbable Silicon Nanomembranes and Iron Catalyst Nanoparticles for Flexible, Transient Electrochemical Dopamine Monitors. *Adv. Healthc. Mater.* **2018**, *7*, 1801071. [[CrossRef](#)] [[PubMed](#)]
30. Li, R.; Qi, H.; Ma, Y.; Deng, Y.; Liu, S.; Jie, Y.; Jing, J.; He, J.; Zhang, X.; Wheatley, L.; et al. A flexible and physically transient electrochemical sensor for real-time wireless nitric oxide monitoring. *Nat. Commun.* **2020**, *11*, 3207. [[CrossRef](#)]
31. Fernandes, C.; Loukopoulos, V.; Smets, J.; Franceschini, F.; Deschaume, O.; Bartic, C.; Ameloot, R.; Ustarroz, J.; Taurino, I. Unraveling the Potential of a Nanostructured Tungsten–Tungsten Oxide Thin Film Electrode as a Bioresorbable Multichemical Wound Healing Monitor. *Adv. Mater. Technol.* **2024**, *9*, 2302007. [[CrossRef](#)]
32. Park, J.-H.; Gu, L.; von Maltzahn, G.; Ruoslahti, E.; Bhatia, S.N.; Sailor, M.J. Biodegradable luminescent porous silicon nanoparticles for in vivo applications. *Nat. Mater.* **2009**, *8*, 331–336. [[CrossRef](#)] [[PubMed](#)]
33. Shin, J.-W.; Kim, D.-J.; Jang, T.-M.; Han, W.B.; Lee, J.H.; Ko, G.-J.; Yang, S.M.; Rajaram, K.; Han, S.; Kang, H.; et al. Highly Elastic, Bioresorbable Polymeric Materials for Stretchable, Transient Electronic Systems. *Nano-Micro Lett.* **2024**, *16*, 102. [[CrossRef](#)] [[PubMed](#)]
34. Bezwada, R.S.; Jamiolkowski, D.D.; Lee, I.-Y.; Agarwal, V.; Persivale, J.; Trenka-Benthin, S.; Erneta, M.; Suryadevara, J.; Yang, A.; Liu, S. Monocryl® suture, a new ultra-pliable absorbable monofilament suture. *Biomaterials* **1995**, *16*, 1141–1148. [[CrossRef](#)] [[PubMed](#)]
35. Lee, S.H.; Kim, B.S.; Kim, S.H.; Choi, S.W.; Jeong, S.I.; Kwon, I.K.; Kang, S.W.; Nikolovski, J.; Mooney, D.J.; Han, Y.K.; et al. Elastic biodegradable poly (glycolide-co-caprolactone) scaffold for tissue engineering. *J. Biomed. Mater. Res. Part A* **2003**, *66*, 29–37. [[CrossRef](#)] [[PubMed](#)]
36. Park, J.-H.; Yoon, H.; Kwak, Y.J.; Wang, C.; Alzahrani, K.M.; Wang, S.; Alzahrani, F.D.H.; Kim, H.M.; Koo, E.; Yoo, J.E. Feasibility and safety of inserting transient biodegradable stents in the pylorus during pylorus-preserving gastrectomy for gastric cancer: A preliminary study in a porcine for proof of concept. *Gastric Cancer* **2023**, *26*, 155–166. [[CrossRef](#)] [[PubMed](#)]
37. Sharma, U.; Concagh, D.; Core, L.; Kuang, Y.; You, C.; Pham, Q.; Zugates, G.; Busold, R.; Webber, S.; Merlo, J.; et al. The development of bioresorbable composite polymeric implants with high mechanical strength. *Nat. Mater.* **2018**, *17*, 96–103. [[CrossRef](#)] [[PubMed](#)]
38. Feili, D.; Schuettler, M.; Doerge, T.; Kammer, S.; Stieglitz, T. Encapsulation of organic field effect transistors for flexible biomedical microimplants. *Sens. Actuators A Phys.* **2005**, *120*, 101–109. [[CrossRef](#)]
39. Lee, J.; Park, S.; Choi, Y. Organic encapsulants for bioresorbable medical electronics. *Mrs Bull.* **2024**, *49*, 247–255. [[CrossRef](#)]
40. Lim, D.; Hong, I.; Park, S.U.; Chae, J.W.; Lee, S.; Baac, H.W.; Shin, C.; Lee, J.; Roh, Y.; Im, C.; et al. Functional Encapsulating Structure for Wireless and Immediate Monitoring of the Fluid Penetration. *Adv. Funct. Mater.* **2022**, *32*, 202201854. [[CrossRef](#)]
41. Fumeaux, N.; Almeida, C.P.; Demuru, S.; Briand, D. Organic electrochemical transistors printed from degradable materials as disposable biochemical sensors. *Sci. Rep.* **2023**, *13*, 11467. [[CrossRef](#)]
42. Xu, M.; Jiang, Y.; Pradhan, S.; Yadavalli, V.K. Use of Silk Proteins to Form Organic, Flexible, Degradable Biosensors for Metabolite Monitoring. *Front. Mater.* **2019**, *6*, 331. [[CrossRef](#)]
43. Gao, H.N.; Zhang, J.H.; Yu, W.L.; Li, Y.F.; Zhu, S.J.; Li, Y.; Wang, T.Q.; Yang, B. Monolithic polyaniline/polyvinyl alcohol nanocomposite actuators with tunable stimuli-responsive properties. *Sens. Actuators B Chem.* **2010**, *145*, 839–846. [[CrossRef](#)]
44. Altin-Yavuzarslan, G.; Sadaba, N.; Brooks, S.M.; Alper, H.S.; Nelson, A. Engineered Living Material Bioreactors with Tunable Mechanical Properties using Vat Photopolymerization. *Small* **2023**, *20*, e2306564. [[CrossRef](#)]
45. Guo, B.C.; Chen, Y.W.; Lei, Y.D.; Zhang, L.Q.; Zhou, W.Y.; Rabie, A.B.M.; Zhao, J.Q. Biobased Poly(propylene sebacate) as Shape Memory Polymer with Tunable Switching Temperature for Potential Biomedical Applications. *Biomacromolecules* **2011**, *12*, 1312–1321. [[CrossRef](#)] [[PubMed](#)]
46. Lang, W.Y.; Huang, H.; Yang, L.; Luo, R.F.; Wang, Y.B.; Xue, B.; Yang, S.G. Polymer Complex Multilayers for Drug Delivery and Medical Devices. *ACS Appl. Bio Mater.* **2023**, *6*, 3555–3565. [[CrossRef](#)] [[PubMed](#)]
47. Hearon, K.; Wierzbicki, M.A.; Nash, L.D.; Landsman, T.L.; Laramy, C.; Lonckecker, A.T.; Gibbons, M.C.; Ur, S.; Cardinal, K.O.; Wilson, T.S.; et al. A Processable Shape Memory Polymer System for Biomedical Applications. *Adv. Healthc. Mater.* **2015**, *4*, 1386–1398. [[CrossRef](#)] [[PubMed](#)]
48. Chiesa, I.; De Maria, C.; Ceccarini, M.R.; Mussolin, L.; Coletta, R.; Morabito, A.; Tonin, R.; Calamai, M.; Morrone, A.; Beccari, T.; et al. 3D Printing Silk-Based Bioresorbable Piezoelectric Self-Adhesive Holey Structures for In Vivo Monitoring on Soft Tissues. *ACS Appl. Mater. Interfaces* **2022**, *14*, 19253–19264. [[CrossRef](#)] [[PubMed](#)]

49. Molinnus, D.; Janus, K.A.; Fang, A.C.; Drinic, A.; Achtsnicht, S.; Köpf, M.; Keusgen, M.; Schöning, M.J. Thick-Film Carbon Electrode Deposited onto a Biodegradable Fibroin Substrate for Biosensing Applications. *Phys. Status Solidi* **2022**, *219*, 2200100. [\[CrossRef\]](#)
50. Presley, K.F.; Falcucci, T.; Shaidani, S.; Fitzpatrick, V.; Barry, J.; Ly, J.T.; Dalton, M.J.; Grusenmeyer, T.A.; Kaplan, D.L. Engineered porosity for tissue-integrating, bioresorbable lifetime-based phosphorescent oxygen sensors. *Biomaterials* **2023**, *301*, 122286. [\[CrossRef\]](#)
51. Kim, H.-J.; Kim, J.-H.; Jun, K.-W.; Kim, J.-H.; Seung, W.-C.; Kwon, O.H.; Park, J.-Y.; Kim, S.-W.; Oh, I.-K. Silk Nanofiber-Networked Bio-Triboelectric Generator: Silk Bio-TEG. *Adv. Energy Mater.* **2016**, *6*, 1502329. [\[CrossRef\]](#)
52. Kaveti, R.; Lee, J.H.; Youn, J.K.; Jang, T.-M.; Han, W.B.; Yang, S.M.; Shin, J.-W.; Ko, G.-J.; Kim, D.-J.; Han, S.; et al. Soft, Long-Lived, Bioresorbable Electronic Surgical Mesh with Wireless Pressure Monitor and On-Demand Drug Delivery. *Adv. Mater.* **2024**, *36*, 2307391. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Shim, J.-S.; Rogers, J.A.; Kang, S.-K. Physically transient electronic materials and devices. *Mater. Sci. Eng. R Rep.* **2021**, *145*, 100624. [\[CrossRef\]](#)
54. Xie, S.; Ren, B.; Gong, G.; Zhang, D.; Chen, Y.; Xu, L.; Zhang, C.; Xu, J.; Zheng, J. Lanthanide-Doped Upconversion Nanoparticle-Cross-Linked Double-Network Hydrogels with Strong Bulk/Interfacial Toughness and Tunable Full-Color Fluorescence for Bioimaging and Biosensing. *ACS Appl. Nano Mater.* **2020**, *3*, 2774–2786. [\[CrossRef\]](#)
55. Cao, Y.; Uhrich, K.E. Biodegradable and biocompatible polymers for electronic applications: A review. *J. Bioact. Compat. Polym.* **2019**, *34*, 3–15. [\[CrossRef\]](#)
56. Falcucci, T.; Presley, K.F.; Choi, J.; Fitzpatrick, V.; Barry, J.; Kishore Sahoo, J.; Ly, J.T.; Grusenmeyer, T.A.; Dalton, M.J.; Kaplan, D.L. Degradable Silk-Based Subcutaneous Oxygen Sensors. *Adv. Funct. Mater.* **2022**, *32*, 2202020. [\[CrossRef\]](#)
57. Chae, J.W.; Lee, D.; Osman, A.; Kang, B.; Hwang, J.; Kim, W.; Kim, D.; Lee, W.H.; Won, S.M. Silk Fibroin, Sericin, and Conductive Silk Composites for Skin-Attachable Transient Electronics. *ACS Appl. Electron. Mater.* **2024**, *6*, 1746–1756. [\[CrossRef\]](#)
58. Ko, G.-J.; Han, S.D.; Kim, J.-K.; Zhu, J.; Han, W.B.; Chung, J.; Yang, S.M.; Cheng, H.; Kim, D.-H.; Kang, C.-Y.; et al. Biodegradable, flexible silicon nanomembrane-based NOx gas sensor system with record-high performance for transient environmental monitors and medical implants. *NPG Asia Mater.* **2020**, *12*, 71. [\[CrossRef\]](#)
59. Soomro, A.M.; Jabbar, F.; Ali, M.; Lee, J.-W.; Mun, S.W.; Choi, K.H. All-range flexible and biocompatible humidity sensor based on poly lactic glycolic acid (PLGA) and its application in human breathing for wearable health monitoring. *J. Mater. Sci. Mater. Electron.* **2019**, *30*, 9455–9465. [\[CrossRef\]](#)
60. Ma, X.; Hu, Q.; Dai, Y.; He, P.; Zhang, X. Disposable sensors based on biodegradable polylactic acid piezoelectret films and their application in wearable electronics. *Sens. Actuators A Phys.* **2022**, *346*, 113834. [\[CrossRef\]](#)
61. Zhang, W.; Liu, P.; Yang, G.; Lei, H. Single Polylactic Acid Nanowire for Highly Sensitive and Multifunctional Optical Biosensing. *ACS Appl. Mater. Interfaces* **2021**, *13*, 27983–27990. [\[CrossRef\]](#)
62. Wang, Y.; Kim, Y.M.; Langer, R. In vivo degradation characteristics of poly(glycerol sebacate). *J. Biomed. Mater. Res. Part A* **2003**, *66A*, 192–197. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Zanjanzadeh Ezazi, N.; Ajdary, R.; Correia, A.; Mäkilä, E.; Salonen, J.; Kemell, M.; Hirvonen, J.; Rojas, O.J.; Ruskoaho, H.J.; Santos, H.A. Fabrication and Characterization of Drug-Loaded Conductive Poly(glycerol sebacate)/Nanoparticle-Based Composite Patch for Myocardial Infarction Applications. *ACS Appl. Mater. Interfaces* **2020**, *12*, 6899–6909. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Curry, E.J.; Ke, K.; Chorsi, M.T.; Wrobel, K.S.; Miller, A.N.; Patel, A.; Kim, I.; Feng, J.; Yue, L.; Wu, Q.; et al. Biodegradable Piezoelectric Force Sensor. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 909–914. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Oh, S.H.; Park, S.C.; Kim, H.K.; Koh, Y.J.; Lee, J.-H.; Lee, M.C.; Lee, J.H. Degradation Behavior of 3D Porous Polydioxanone-b-Polycaprolactone Scaffolds Fabricated Using the Melt-Molding Particulate-Leaching Method. *J. Biomater. Sci. Polym. Ed.* **2011**, *22*, 225–237. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Soto, R.J.; Hall, J.R.; Brown, M.D.; Taylor, J.B.; Schoenfisch, M.H. In Vivo Chemical Sensors: Role of Biocompatibility on Performance and Utility. *Anal. Chem.* **2017**, *89*, 276–299. [\[CrossRef\]](#)
67. Zhang, J.; Xie, B.; Xi, Z.; Zhao, L.; Cen, L.; Yang, Y. A comparable study of polyglycolic acid's degradation on macrophages' activation. *Mater. Sci. Eng. C* **2020**, *109*, 110574. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Takaoka, H.; Yasuzawa, M. Fabrication of an Implantable Fine Needle-Type Glucose Sensor Using  $\gamma$ -Polyglutamic Acid. *Anal. Sci.* **2010**, *26*, 551–555. [\[CrossRef\]](#)
69. Özcan, B.; Sezgintürk, M.K. A novel and disposable GP- based impedimetric biosensor using electropolymerization process with PGA for highly sensitive determination of leptin: Early diagnosis of childhood obesity. *Talanta* **2021**, *225*, 121985. [\[CrossRef\]](#)
70. Hwang, S.-W.; Lee, C.H.; Cheng, H.; Jeong, J.-W.; Kang, S.-K.; Kim, J.-H.; Shin, J.; Yang, J.; Liu, Z.; Ameer, G.A.; et al. Biodegradable Elastomers and Silicon Nanomembranes/Nanoribbons for Stretchable, Transient Electronics, and Biosensors. *Nano Lett.* **2015**, *15*, 2801–2808. [\[CrossRef\]](#)
71. Beyene, A.G.; Demirel, G.S.; Landry, M.P. Nanoparticle-Templated Molecular Recognition Platforms for Detection of Biological Analytes. *Curr. Protoc. Chem. Biol.* **2016**, *8*, 197–223. [\[CrossRef\]](#)
72. Piacenti da Silva, M.; Fernandes, J.C.; de Figueiredo, N.B.; Congiu, M.; Mulato, M.; de Oliveira Graeff, C.F. Melanin as an active layer in biosensors. *AIP Adv.* **2014**, *4*, 037120. [\[CrossRef\]](#)
73. Ozlu, B.; Shim, B.S. Highly Conductive Melanin-like Polymer Composites for Nonenzymatic Glucose Biosensors with a Wide Detection Range. *ACS Appl. Polym. Mater.* **2022**, *4*, 2527–2535. [\[CrossRef\]](#)

74. Lin, S.; Yuk, H.; Zhang, T.; Parada, G.A.; Koo, H.; Yu, C.; Zhao, X. Stretchable Hydrogel Electronics and Devices. *Adv. Mater.* **2016**, *28*, 4497–4505. [[CrossRef](#)] [[PubMed](#)]
75. Zhao, W.; Zhou, H.; Li, W.; Chen, M.; Zhou, M.; Zhao, L. An Environment-Tolerant Ion-Conducting Double-Network Composite Hydrogel for High-Performance Flexible Electronic Devices. *Nano-Micro Lett.* **2024**, *16*, 99. [[CrossRef](#)] [[PubMed](#)]
76. Chen, J.; Yang, Z.; Shi, D.; Zhou, T.; Kaneko, D.; Chen, M. High strength and toughness of double physically cross-linked hydrogels composed of polyvinyl alcohol and calcium alginate. *J. Appl. Polym. Sci.* **2021**, *138*, 49987. [[CrossRef](#)]
77. Gong, J.P.; Katsuyama, Y.; Kurokawa, T.; Osada, Y. Double-Network Hydrogels with Extremely High Mechanical Strength. *Adv. Mater.* **2003**, *15*, 1155–1158. [[CrossRef](#)]
78. Sun, J.Y.; Zhao, X.; Illeperuma, W.R.; Chaudhuri, O.; Oh, K.H.; Mooney, D.J.; Vlassak, J.J.; Suo, Z. Highly stretchable and tough hydrogels. *Nature* **2012**, *489*, 133–136. [[CrossRef](#)] [[PubMed](#)]
79. Xu, Z.; Chen, Y.; Cao, Y.; Xue, B. Tough Hydrogels with Different Toughening Mechanisms and Applications. *Int. J. Mol. Sci.* **2024**, *25*, 2675. [[CrossRef](#)]
80. Zhao, X. Multi-scale multi-mechanism design of tough hydrogels: Building dissipation into stretchy networks. *Soft Matter* **2014**, *10*, 672–687. [[CrossRef](#)]
81. Zhu, R.; Zhu, D.; Zheng, Z.; Wang, X. Tough double network hydrogels with rapid self-reinforcement and low hysteresis based on highly entangled networks. *Nat. Commun.* **2024**, *15*, 1344. [[CrossRef](#)]
82. Yang, Q.; Wei, T.; Yin, R.T.; Wu, M.; Xu, Y.; Koo, J.; Choi, Y.S.; Xie, Z.; Chen, S.W.; Kandela, I.; et al. Photocurable bioresorbable adhesives as functional interfaces between flexible bioelectronic devices and soft biological tissues. *Nat. Mater.* **2021**, *20*, 1559–1570. [[CrossRef](#)] [[PubMed](#)]
83. Kim, B.; Park, J.; Lee, J.Y. Conductive double-network hydrogel composed of sodium alginate, polyacrylamide, and reduced graphene oxide. *Korean J. Chem. Eng.* **2023**, *40*, 352–360. [[CrossRef](#)]
84. Zhang, X.; Deng, J.-N.; Yang, K.; Li, Q.; Meng, S.-Y.; Sun, X.-X.; Song, Z.-Z.; Tian, Y.-D.; Zhang, S.-A.; Liu, X.-J.; et al. High-strength and self-degradable sodium alginate/polyacrylamide preformed particle gels for conformance control to enhance oil recovery. *Pet. Sci.* **2022**, *19*, 3149–3158. [[CrossRef](#)]
85. Cao, Q.; Shu, Z.; Zhang, T.; Ji, W.; Chen, J.; Wei, Y. Highly Elastic, Sensitive, Stretchable, and Skin-Inspired Conductive Sodium Alginate/Polyacrylamide/Gallium Composite Hydrogel with Toughness as a Flexible Strain Sensor. *Biomacromolecules* **2022**, *23*, 2603–2613. [[CrossRef](#)] [[PubMed](#)]
86. Darvishi, S.; Souissi, M.; Kharaziha, M.; Karimzadeh, F.; Sahara, R.; Ahadian, S. Gelatin methacryloyl hydrogel for glucose biosensing using Ni nanoparticles-reduced graphene oxide: An experimental and modeling study. *Electrochim. Acta* **2018**, *261*, 275–283. [[CrossRef](#)]
87. Zhu, M.; Wang, Y.; Ferracci, G.; Zheng, J.; Cho, N.-J.; Lee, B.H. Gelatin methacryloyl and its hydrogels with an exceptional degree of controllability and batch-to-batch consistency. *Sci. Rep.* **2019**, *9*, 6863. [[CrossRef](#)] [[PubMed](#)]
88. Naficy, S.; Oveissi, F.; Patrick, B.; Schindeler, A.; Dehghani, F. Printed, Flexible pH Sensor Hydrogels for Wet Environments. *Adv. Mater. Technol.* **2018**, *3*, 1800137. [[CrossRef](#)]
89. Teo, M.Y.; Lim, K.; Aw, K.C.; Kee, S.; Stringer, J. Towards biodegradable conducting polymers by incorporating seaweed cellulose for decomposable wearable heaters. *RSC Adv.* **2023**, *13*, 26267–26274. [[CrossRef](#)] [[PubMed](#)]
90. Zhu, C.; Bing, Y.; Chen, Q.; Pang, B.; Li, J.; Zhang, T. Nonenzymatic Flexible Wearable Biosensors for Vitamin C Monitoring in Sweat. *ACS Appl. Mater. Interfaces* **2023**, *15*, 19384–19392. [[CrossRef](#)]
91. Ballabio, M.; Zhang, T.; Chen, C.; Zhang, P.; Liao, Z.; Hambsch, M.; Mannsfeld, S.C.B.; Zschech, E.; Sirringhaus, H.; Feng, X.; et al. Band-Like Charge Transport in Phytic Acid-Doped Polyaniline Thin Films. *Adv. Funct. Mater.* **2021**, *31*, 2105184. [[CrossRef](#)]
92. Wang, C.; Zhang, J.; Xu, H.; Huang, C.; Lu, Y.; Cui, H.; Tan, Y. Chitosan-driven biocompatible hydrogel based on water-soluble polypyrrole for stable human-machine interfaces. *Carbohydr. Polym.* **2022**, *295*, 119890. [[CrossRef](#)]
93. Mill, T.; Mabey, W. Hydrolysis of Organic Chemicals. In *Reactions and Processes*; Barraclough, P.B., Crossland, N.O., Herrmann, R., Mabey, W., Menzie, C.M., Mill, T., Tinker, P.B., Waldichuk, M., Wolff, C.J.M., Eds.; Springer: Berlin/Heidelberg, Germany, 1988; pp. 71–111.
94. Mabey, W.; Mill, T. Critical review of hydrolysis of organic compounds in water under environmental conditions. *J. Phys. Chem. Ref. Data* **1978**, *7*, 383–415. [[CrossRef](#)]
95. Verma, H.; Aggarwal, M.; Kumar, S. Opportunities and Significance of Nanoparticle-DNA Binding in Medical Biotechnology: A Review. *Cureus* **2022**, *14*, e31005. [[CrossRef](#)]
96. Rosi, N.L.; Mirkin, C.A. Nanostructures in Biodiagnostics. *Chem. Rev.* **2005**, *105*, 1547–1562. [[CrossRef](#)]
97. Lin, J.; Song, T.; Liu, Z.; Yang, D.; Xiang, R.; Hua, W.; Wan, H. Effects of biodegradable biomedical porous MnO<sub>2</sub> nanoparticles on blood components and functions. *Colloids Surf. B Biointerfaces* **2022**, *217*, 112667. [[CrossRef](#)]
98. Rahman, B.M.A.; Viphavakit, C.; Chitree, R.; Ghosh, S.; Pathak, A.K.; Verma, S.; Sakda, N. Optical Fiber, Nanomaterial, and THz-Metasurface-Mediated Nano-Biosensors: A Review. *Biosensors* **2022**, *12*, 42. [[CrossRef](#)] [[PubMed](#)]
99. Jeevanandam, J.; Barhoum, A.; Chan, Y.S.; Dufresne, A.; Danquah, M.K. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. *Beilstein J. Nanotechnol.* **2018**, *9*, 1050–1074. [[CrossRef](#)] [[PubMed](#)]
100. Carlander, U.; Midander, K.; Hedberg, Y.S.; Johanson, G.; Bottai, M.; Karlsson, H.L. Macrophage-Assisted Dissolution of Gold Nanoparticles. *ACS Appl. Bio Mater.* **2019**, *2*, 1006–1016. [[CrossRef](#)] [[PubMed](#)]

101. Oldak, L.; Zielinska, Z.; Socha, K.; Bogdan, S.; Gorodkiewicz, E. Phospho-Tau 181 quantification method for Alzheimer's disease based on an array 2D biosensor combined with surface plasmon resonance imaging. *Talanta* **2024**, *271*, 125736. [\[CrossRef\]](#)
102. Wang, Y.; Sun, B.; Wei, H.; Li, Y.; Hu, F.; Du, X.; Chen, J. Investigating immunosensor for determination of depression marker-Apo-A4 based on patterning AuNPs and N-Gr nanomaterials onto ITO-PET flexible electrodes with amplifying signal. *Anal. Chim. Acta* **2022**, *1224*, 340217. [\[CrossRef\]](#)
103. Jayakumar, K.; Bennett, R.; Leech, D. Electrochemical glucose biosensor based on an osmium redox polymer and glucose oxidase grafted to carbon nanotubes: A design-of-experiments optimisation of current density and stability. *Electrochim. Acta* **2021**, *371*, 137845. [\[CrossRef\]](#)
104. Shrestha, D.; Kang, K.; Nayaju, T.; Bacirhonde, P.M.; Maharjan, B.; Park, C.H.; Kim, C.S. Co<sub>1.22</sub>Ni<sub>x</sub>O<sub>4</sub>/fMWCNTs-hybrid nanocomposite-based self-adhesive wearable non-enzymatic electrochemical sensor for continuous glucose monitoring in sweat. *Colloids Surf. A Physicochem. Eng. Asp.* **2024**, *686*, 133361. [\[CrossRef\]](#)
105. Franklin, D.; Ueltschi, T.; Carlini, A.; Yao, S.; Reeder, J.; Richards, B.; Van Duyne, R.P.; Rogers, J.A. Bioresorbable Microdroplet Lasers as Injectable Systems for Transient Thermal Sensing and Modulation. *ACS Nano* **2021**, *15*, 2327–2339. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Zhao, P.; Zhang, H.; Sun, X.; Hao, S.; Dong, S. A hybrid bioelectrochemical device based on glucose/O<sub>2</sub> enzymatic biofuel cell for energy conversion and storage. *Electrochim. Acta* **2022**, *420*, 140440. [\[CrossRef\]](#)
107. Yu, K.J.; Kuzum, D.; Hwang, S.-W.; Kim, B.H.; Juul, H.; Kim, N.H.; Won, S.M.; Chiang, K.; Trumpis, M.; Richardson, A.G.; et al. Bioresorbable silicon electronics for transient spatiotemporal mapping of electrical activity from the cerebral cortex. *Nat. Mater.* **2016**, *15*, 782–791. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Jin, X.; Jiang, H.; Zhang, Z.; Yao, Y.; Bao, X.; Hu, Q. Ultrastretchable, self-adhesive, strain-sensitive and self-healing GO@DA/Alginate/P(AAc-co-AAm) multifunctional hydrogels via mussel-inspired chemistry. *Carbohydr. Polym.* **2021**, *254*, 117316. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Liu, Y.; Zhu, S.; Gu, Z.; Chen, C.; Zhao, Y. Toxicity of manufactured nanomaterials. *Particuology* **2022**, *69*, 31–48. [\[CrossRef\]](#)
110. Zhang, A.; Meng, K.; Liu, Y.; Pan, Y.; Qu, W.; Chen, D.; Xie, S. Absorption, distribution, metabolism, and excretion of nanocarriers in vivo and their influences. *Adv. Colloid Interface Sci.* **2020**, *284*, 102261. [\[CrossRef\]](#) [\[PubMed\]](#)
111. Riaz Ahmed, K.B.; Nagy, A.M.; Brown, R.P.; Zhang, Q.; Malghan, S.G.; Goering, P.L. Silver nanoparticles: Significance of physicochemical properties and assay interference on the interpretation of in vitro cytotoxicity studies. *Toxicol. In Vitro* **2017**, *38*, 179–192. [\[CrossRef\]](#)
112. Hwang, S.-W.; Kim, D.-H.; Tao, H.; Kim, T.-i.; Kim, S.; Yu, K.J.; Panilaitis, B.; Jeong, J.-W.; Song, J.-K.; Omenetto, F.G.; et al. Materials and Fabrication Processes for Transient and Bioresorbable High-Performance Electronics. *Adv. Funct. Mater.* **2013**, *23*, 4087–4093. [\[CrossRef\]](#)
113. Palmroth, A.; Salpavaara, T.; Vuoristo, P.; Karjalainen, S.; Kääriäinen, T.; Miettinen, S.; Massera, J.; Lekkala, J.; Kellomäki, M. Materials and Orthopedic Applications for Bioresorbable Inductively Coupled Resonance Sensors. *ACS Appl. Mater. Interfaces* **2020**, *12*, 31148–31161. [\[CrossRef\]](#)
114. Helmersson, U.; Lättemann, M.; Bohlmark, J.; Ehasarian, A.P.; Gudmundsson, J.T. Ionized physical vapor deposition (IPVD): A review of technology and applications. *Thin Solid Films* **2006**, *513*, 1–24. [\[CrossRef\]](#)
115. Schuettler, M.; Stiess, S.; King, B.V.; Suaning, G.J. Fabrication of implantable microelectrode arrays by laser cutting of silicone rubber and platinum foil\*. *J. Neural Eng.* **2005**, *2*, S121. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Huang, Q.; Zhu, Y. Printing conductive nanomaterials for flexible and stretchable electronics: A review of materials, processes, and applications. *Adv. Mater. Technol.* **2019**, *4*, 1800546. [\[CrossRef\]](#)
117. Zavanelli, N.; Yeo, W.-H. Advances in screen printing of conductive nanomaterials for stretchable electronics. *ACS Omega* **2021**, *6*, 9344–9351. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Secor, E.B. Electronics, P. Principles of aerosol jet printing. *Flex. Print. Electron.* **2018**, *3*, 035002. [\[CrossRef\]](#)
119. Hales, S.; Tokita, E.; Neupane, R.; Ghosh, U.; Elder, B.; Wirthlin, D.; Kong, Y.L. 3D printed nanomaterial-based electronic, biomedical, and bioelectronic devices. *Nanotechnology* **2020**, *31*, 172001. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Prabhakar, P.; Sen, R.K.; Dwivedi, N.; Khan, R.; Solanki, P.R.; Srivastava, A.K.; Dhand, C. 3D-Printed Microfluidics and Potential Biomedical Applications. *Front. Nanotechnol.* **2021**, *3*, 609355. [\[CrossRef\]](#)
121. Zhu, Y.Z.; Joralmón, D.; Shan, W.T.; Chen, Y.Y.; Rong, J.H.; Zhao, H.Y.; Xiao, S.Q.; Li, X.J. 3D printing biomimetic materials and structures for biomedical applications. *Bio-Design Manuf.* **2021**, *4*, 405–428. [\[CrossRef\]](#)
122. Li, J.; Luo, S.; Liu, J.; Xu, H.; Huang, X. Processing Techniques for Bioresorbable Nanoparticles in Fabricating Flexible Conductive Interconnects. *Materials* **2018**, *11*, 1102. [\[CrossRef\]](#)
123. Shou, W.; Mahajan, B.K.; Ludwig, B.; Yu, X.; Staggs, J.; Huang, X.; Pan, H. Low-Cost Manufacturing of Bioresorbable Conductors by Evaporation–Condensation-Mediated Laser Printing and Sintering of Zn Nanoparticles. *Adv. Mater.* **2017**, *29*, 1700172. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Yang, Q.; Hu, Z.; Seo, M.-H.; Xu, Y.; Yan, Y.; Hsu, Y.-H.; Berkovich, J.; Lee, K.; Liu, T.-L.; McDonald, S. High-speed, scanned laser structuring of multi-layered eco/bioresorbable materials for advanced electronic systems. *Nat. Commun.* **2022**, *13*, 6518. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Wu, Y.; Rytkin, E.; Bimrose, M.; Li, S.; Choi, Y.S.; Lee, G.; Wang, Y.; Tang, L.; Madrid, M.; Wickerson, G.; et al. A Sewing Approach to the Fabrication of Eco/bioresorbable Electronics. *Small* **2023**, *19*, 2305017. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Klonoff, D.C. Technology. The benefits of implanted glucose sensors. *J. Diabetes Sci. Technol.* **2007**, *1*, 797–800. [\[CrossRef\]](#) [\[PubMed\]](#)

127. Luo, X.; Yu, Q.; Liu, Y.; Gai, W.; Ye, L.; Yang, L.; Cui, Y. Closed-Loop Diabetes Minipatch Based on a Biosensor and an Electroosmotic Pump on Hollow Biodegradable Microneedles. *ACS Sens.* **2022**, *7*, 1347–1360. [[CrossRef](#)] [[PubMed](#)]
128. Fang, Y.; Wang, S.; Liu, Y.; Xu, Z.; Zhang, K.; Guo, Y. Development of Cu nanoflowers modified the flexible needle-type microelectrode and its application in continuous monitoring glucose in vivo. *Biosens. Bioelectron.* **2018**, *110*, 44–51. [[CrossRef](#)]
129. Bai, W.; Yang, H.; Ma, Y.; Chen, H.; Shin, J.; Liu, Y.; Yang, Q.; Kandela, I.; Liu, Z.; Kang, S.-K.; et al. Flexible Transient Optical Waveguides and Surface-Wave Biosensors Constructed from Monocrystalline Silicon. *Adv. Mater.* **2018**, *30*, 1801584. [[CrossRef](#)]
130. Mehrotra, S.; Rai, P.; Gautam, K.; Saxena, A.; Verma, R.; Lahane, V.; Singh, S.; Yadav, A.K.; Patnaik, S.; Anbumani, S.; et al. Chitosan-carbon nanofiber based disposable bioelectrode for electrochemical detection of oxytocin. *Food Chem.* **2023**, *418*, 135965. [[CrossRef](#)]
131. Xu, M.; Yadavalli, V.K. Flexible Biosensors for the Impedimetric Detection of Protein Targets Using Silk-Conductive Polymer Biocomposites. *ACS Sens.* **2019**, *4*, 1040–1047. [[CrossRef](#)]
132. Xie, X.; Zhang, W.; Abbaspourrad, A.; Ahn, J.; Bader, A.; Bose, S.; Vegas, A.; Lin, J.; Tao, J.; Hang, T.; et al. Microfluidic Fabrication of Colloidal Nanomaterials-Encapsulated Microcapsules for Biomolecular Sensing. *Nano Lett.* **2017**, *17*, 2015–2020. [[CrossRef](#)]
133. Nitzan, M.; Romem, A.; Koppel, R. Pulse oximetry: Fundamentals and technology update. *Med Devices Evid. Res.* **2014**, *7*, 231–239. [[CrossRef](#)] [[PubMed](#)]
134. Chan, E.D.; Chan, M.M.; Chan, M.M. Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations. *Respir. Med.* **2013**, *107*, 789–799. [[CrossRef](#)] [[PubMed](#)]
135. Lu, W.; Bai, W.; Zhang, H.; Xu, C.; Chiarelli, A.M.; Vázquez-Guardado, A.; Xie, Z.; Shen, H.; Nandoliya, K.; Zhao, H.; et al. Wireless, implantable catheter-type oximeter designed for cardiac oxygen saturation. *Sci. Adv.* **2021**, *7*, eabe0579. [[CrossRef](#)] [[PubMed](#)]
136. Kahlert, H. Functionalized carbon electrodes for pH determination. *J. Solid State Electrochem.* **2008**, *12*, 1255–1266. [[CrossRef](#)]
137. Andrews, R.J.; Bringas, J.R.; Alonzo, G. Cerebrospinal fluid pH and PCO<sub>2</sub> rapidly follow arterial blood pH and PCO<sub>2</sub> with changes in ventilation. *Neurosurgery* **1994**, *34*, 466–470. [[CrossRef](#)] [[PubMed](#)]
138. Wijayarathna, U.N.; Kiridena, S.D.; Adams, J.D.; Behrend, C.J.; Anker, J.N. Synovial Fluid pH Sensor for Early Detection of Prosthetic Hip Infections. *Adv. Funct. Mater.* **2021**, *31*, 2104124. [[CrossRef](#)]
139. Swietach, P.; Vaughan-Jones, R.D.; Harris, A.L.; Hulikova, A. The chemistry, physiology and pathology of pH in cancer. *Philos. Trans. R. Soc. B Biol. Sci.* **2014**, *369*, 20130099. [[CrossRef](#)]
140. Ghoneim, M.T.; Nguyen, A.; Dereje, N.; Huang, J.; Moore, G.C.; Murzynowski, P.J.; Dagdeviren, C. Recent Progress in Electrochemical pH-Sensing Materials and Configurations for Biomedical Applications. *Chem. Rev.* **2019**, *119*, 5248–5297. [[CrossRef](#)] [[PubMed](#)]
141. Paghi, A.; Corsi, M.; La Mattina, A.A.; Egri, G.; Dähne, L.; Barillaro, G. Wireless and Flexible Optoelectronic System for In Situ Monitoring of Vaginal pH Using a Bioresorbable Fluorescence Sensor. *Adv. Mater. Technol.* **2023**, *8*, 2201600. [[CrossRef](#)]
142. Girard, E.; Messenger, M.; Sauvanet, A.; Benoist, S.; Piessen, G.; Mabrut, J.Y.; Mariette, C. Anastomotic leakage after gastrointestinal surgery: Diagnosis and management. *J. Visc. Surg.* **2014**, *151*, 441–450. [[CrossRef](#)]
143. Chou, S.-C.; Hsieh, Y.-C.; Cheang, W.-H.; Sun, B.-Y.; Chu, C.-Y.; Chen, S.-Y.; Chiao, J.-C.; Wu, P.-W. A flexible IrO<sub>2</sub> membrane for pH sensing. *Sci. Rep.* **2022**, *12*, 11712. [[CrossRef](#)] [[PubMed](#)]
144. Drozdov, A.D.; deClaville Christiansen, J. Modeling the effects of pH and ionic strength on swelling of polyelectrolyte gels. *J. Chem. Phys.* **2015**, *142*, 114904. [[CrossRef](#)] [[PubMed](#)]
145. Philippova, O.E.; Hourdet, D.; Audebert, R.; Khokhlov, A.R. pH-Responsive Gels of Hydrophobically Modified Poly(acrylic acid). *Macromolecules* **1997**, *30*, 8278–8285. [[CrossRef](#)]
146. Li, S.; Lu, D.; Li, S.; Liu, J.; Xu, Y.; Yan, Y.; Rodriguez, J.Z.; Bai, H.; Avila, R.; Kang, S.; et al. Bioresorbable, wireless, passive sensors for continuous pH measurements and early detection of gastric leakage. *Sci. Adv.* **2024**, *10*, eadj0268. [[CrossRef](#)] [[PubMed](#)]
147. Gurkov, A.; Sadovoy, A.; Shchapova, E.; Teh, C.; Meglinski, I.; Timofeyev, M. Microencapsulated fluorescent pH probe as implantable sensor for monitoring the physiological state of fish embryos. *PLoS ONE* **2017**, *12*, e0186548. [[CrossRef](#)]
148. Sadovoy, A.; Teh, C.; Korzh, V.; Escobar, M.; Meglinski, I. Microencapsulated bio-markers for assessment of stress conditions in aquatic organisms in vivo. *Laser Phys. Lett.* **2012**, *9*, 542. [[CrossRef](#)]
149. Yu, K.-K.; Li, K.; Hou, J.-T.; Yang, J.; Xie, Y.-M.; Yu, X.-Q. Rhodamine based pH-sensitive “intelligent” polymers as lysosome targeting probes and their imaging applications in vivo. *Polym. Chem.* **2014**, *5*, 5804–5812. [[CrossRef](#)]
150. Arman Kuzubasoglu, B.; Kursun Bahadir, S. Flexible temperature sensors: A review. *Sens. Actuators A Phys.* **2020**, *315*, 112282. [[CrossRef](#)]
151. Lu, D.; Yan, Y.; Avila, R.; Kandela, I.; Stepien, I.; Seo, M.-H.; Bai, W.; Yang, Q.; Li, C.; Haney, C.R.; et al. Bioresorbable, Wireless, Passive Sensors as Temporary Implants for Monitoring Regional Body Temperature. *Adv. Healthc. Mater.* **2020**, *9*, 2000942. [[CrossRef](#)]
152. Bai, W.; Irie, M.; Liu, Z.; Luan, H.; Franklin, D.; Nandoliya, K.; Guo, H.; Zang, H.; Weng, Y.; Lu, D.; et al. Bioresorbable Multilayer Photonic Cavities as Temporary Implants for Tether-Free Measurements of Regional Tissue Temperatures. *BME Front.* **2021**, *2021*, 8653218. [[CrossRef](#)]
153. Shin, J.; Liu, Z.; Bai, W.; Liu, Y.; Yan, Y.; Xue, Y.; Kandela, I.; Pezhouh, M.; MacEwan, M.R.; Huang, Y.; et al. Bioresorbable optical sensor systems for monitoring of intracranial pressure and temperature. *Sci. Adv.* **2019**, *5*, eaaw1899. [[CrossRef](#)] [[PubMed](#)]
154. Ouyang, H.; Li, Z.; Gu, M.; Hu, Y.; Xu, L.; Jiang, D.; Cheng, S.; Zou, Y.; Deng, Y.; Shi, B.; et al. A Bioresorbable Dynamic Pressure Sensor for Cardiovascular Postoperative Care. *Adv. Mater.* **2021**, *33*, 2102302. [[CrossRef](#)]

155. Abramson, A.; Chan, C.T.; Khan, Y.; Mermin-Bunnell, A.; Matsuhisa, N.; Fong, R.; Shad, R.; Hiesinger, W.; Mallick, P.; Gambhir, S.S.; et al. A flexible electronic strain sensor for the real-time monitoring of tumor regression. *Sci. Adv.* **2022**, *8*, eabn6550. [CrossRef]
156. Yu, X.; Wang, H.; Ning, X.; Sun, R.; Albadawi, H.; Salomao, M.; Silva, A.C.; Yu, Y.; Tian, L.; Koh, A.; et al. Needle-shaped ultrathin piezoelectric microsystem for guided tissue targeting via mechanical sensing. *Nat. Biomed. Eng.* **2018**, *2*, 165–172. [CrossRef]
157. Li, Z.; Li, C.; Deng, Y. Bioresorbable Pressure Sensor and Its Applications in Abnormal Respiratory Event Identification. *ACS Appl. Electron. Mater.* **2023**, *5*, 1761–1769. [CrossRef]
158. Qiao, Z.; Miele, M.; Ji, H.-F. Injectable and moldable hydrogels for use in sensitive and wide range strain sensing applications. *Biopolymers* **2020**, *111*, e23355. [CrossRef]
159. Kang, M.; Park, J.; Kim, S.A.; Kim, T.Y.; Kim, J.Y.; Kim, D.W.; Park, K.; Seo, J. Modulus-tunable multifunctional hydrogel ink with nanofillers for 3D-Printed soft electronics. *Biosens. Bioelectron.* **2024**, *255*, 116257. [CrossRef] [PubMed]
160. What Does the Nervous System Do? Available online: <https://www.nichd.nih.gov/health/topics/neuro/conditioninfo/functions> (accessed on 25 June 2024).
161. Lu, D.; Yan, Y.; Deng, Y.; Yang, Q.; Zhao, J.; Seo, M.-H.; Bai, W.; MacEwan, M.R.; Huang, Y.; Ray, W.Z.; et al. Bioresorbable Wireless Sensors as Temporary Implants for In Vivo Measurements of Pressure. *Adv. Funct. Mater.* **2020**, *30*, 2003754. [CrossRef]
162. Shin, J.; Yan, Y.; Bai, W.; Xue, Y.; Gamble, P.; Tian, L.; Kandela, I.; Haney, C.R.; Spees, W.; Lee, Y.; et al. Bioresorbable pressure sensors protected with thermally grown silicon dioxide for the monitoring of chronic diseases and healing processes. *Nat. Biomed. Eng.* **2019**, *3*, 37–46. [CrossRef]
163. Wu, X.; Feng, J.; Deng, J.; Cui, Z.; Wang, L.; Xie, S.; Chen, C.; Tang, C.; Han, Z.; Yu, H.; et al. Fiber-shaped organic electrochemical transistors for biochemical detections with high sensitivity and stability. *Sci. China Chem.* **2020**, *63*, 1281–1288. [CrossRef]
164. Xu, K.; Li, S.; Dong, S.; Zhang, S.; Pan, G.; Wang, G.; Shi, L.; Guo, W.; Yu, C.; Luo, J. Bioresorbable Electrode Array for Electrophysiological and Pressure Signal Recording in the Brain. *Adv. Healthc. Mater.* **2019**, *8*, e1801649. [CrossRef]
165. Xie, J.; Dai, Y.; Xing, Y.; Wang, Y.; Yang, G.; He, E.; Xu, Z.; Fan, P.; Mo, F.; Wu, Y.; et al. PtNPs/rGO-GluOx/MPD Directionally Electroplated Dual-Mode Microelectrode Arrays for Detecting the Synergistic Relationship between the Cortex and Hippocampus of Epileptic Rats. *ACS Sens.* **2023**, *8*, 1810–1818. [CrossRef]
166. Macdonald, T.J.; Lanzetta, L.; Liang, X.; Ding, D.; Haque, S.A. Engineering Stable Lead-Free Tin Halide Perovskite Solar Cells: Lessons from Materials Chemistry. *Adv. Mater.* **2023**, *35*, e2206684. [CrossRef]
167. Institute of Medicine (US) Panel on Micronutrients. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*; National Academies Press (US): Washington, DC, USA, 2001.
168. Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference, Intakes. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*; National Academies Press (US): Washington, DC, USA, 1997.
169. Su, H.; Wang, Y.; Gu, Y.; Bowman, L.; Zhao, J.; Ding, M. Potential applications and human biosafety of nanomaterials used in nanomedicine. *J. Appl. Toxicol. JAT* **2018**, *38*, 3–24. [CrossRef] [PubMed]
170. Sigurdsson, S.A.; Yu, Z.; Lee, J.; Nurmikko, A. A method for large-scale implantation of 3D microdevice ensembles into brain and soft tissue. *Microsyst. Nanoeng.* **2020**, *6*, 97. [CrossRef]
171. Yuk, H.; Varela, C.E.; Nabzdyk, C.S.; Mao, X.; Padera, R.F.; Roche, E.T.; Zhao, X. Dry double-sided tape for adhesion of wet tissues and devices. *Nature* **2019**, *575*, 169–174. [CrossRef] [PubMed]
172. Kang, S.-K.; Murphy, R.K.J.; Hwang, S.-W.; Lee, S.M.; Harburg, D.V.; Krueger, N.A.; Shin, J.; Gamble, P.; Cheng, H.; Yu, S.; et al. Bioresorbable silicon electronic sensors for the brain. *Nature* **2016**, *530*, 71–76. [CrossRef] [PubMed]
173. Lacava, A.; Zottola, V.; Bonaldo, A.; Cuomo, F.; Basagni, S. Securing Bluetooth Low Energy networking: An overview of security procedures and threats. *Comput. Netw.* **2022**, *211*, 108953. [CrossRef]
174. Cope, P.; Campbell, J.; Hayajneh, T. An investigation of Bluetooth security vulnerabilities. In Proceedings of the 2017 IEEE 7th Annual Computing and Communication Workshop and Conference (CCWC), Las Vegas, NV, USA, 9–11 January 2017; pp. 1–7.
175. Krzysztoń, M.; Marks, M. Simulation of watchdog placement for cooperative anomaly detection in Bluetooth Mesh Intrusion Detection System. *Simul. Model. Pract. Theory* **2020**, *101*, 102041. [CrossRef]
176. Lacava, A.; Giacomini, E.; Alterio, F.D.; Cuomo, F. Intrusion Detection System for Bluetooth Mesh Networks: Data Gathering and Experimental Evaluations. In Proceedings of the 2021 IEEE International Conference on Pervasive Computing and Communications Workshops and other Affiliated Events (PerCom Workshops), Kassel, Germany, 22–26 March 2021; pp. 661–666.

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.