REVIEW

Biointerfaced sensors for biodiagnostics

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ABSTRACT
Biointerfaced sensors have emerged as a new paradigm for medical applications that require an interface and/or intimate contact with biological components/systems such as cells, tissues, and whole organs. This article provides a review of the concept, design, and device characteristics of biointerfaced sensors needed for successful implementation of biodiagnostics and monitoring. It begins by presenting and discussing the different considerations that arise from artificial interfaces with different biological environments. It then explores the main strategies for sensor and material design, while highlighting the required chemistry, structure, and mechanical properties needed to maintain an unperturbed interface with the surrounding biological environment. Finally, the review discusses successful state-of-the-art demonstrations of body monitoring and biodiagnostics, focusing on the brain, heart, muscles, skin, teeth, and other tissues for medical purposes. Insights, perspectives, and recommendations for future research are presented.

KEYWORDS
biodiagnostics, epidermal, implantable, monitoring, sensor, wearable

1 | INTRODUCTION

Biointerfaced sensors have been attracting interest in recent years due to their promising integration in healthcare and medical systems.[1–3] Such sensors refer to sensing devices that interface with biological components/systems such as cells, tissues, and whole organs. Of the many possible applications for biointerfaced sensors, body monitoring for diagnostic applications has garnered the most attention. The rationale behind this application category relies on the fact that human bodily conditions and disorders are associated with specific chemical/biological/physical stimuli[4,5] that can be visualized and measured using these sensors, which should eventually allow innovative, sensitive, and fast biodiagnostic techniques.

Biointerfaced sensors can be classified into three main groups based on their invasiveness, which affects their function and biocompatibility requirements. The first group includes noninvasive biointerfaced sensors,[3,6] viz. sensors that are external to the body and usually analyze naturally excreted liquids and gases. Among the sensors are wearable devices that measure sweat components,[7] tooth implants monitoring saliva,[8] contact-lens sensors monitoring tears,[9] ingestible electronics,[10] and more. While biocompatibility concerns are simple in these...
configurations, noninvasive sensors cannot be utilized in biodiagnostic applications in which the target stimuli are highly localized inside the body (eg, monitoring the heart’s mechanical properties).[5] The second category includes invasive sensors,[11] viz. sensors that can be situated inside the body and have intimate contact with blood and extracellular fluids or a specific organ. Since the concentration of biomarkers or stimuli is larger near the tissue surface, the intimate contact between sensors and tissues usually reveals highly sensitive signals. However, the same contact raises concerns of foreign body response (FBR) and biocompatibility issues that prevent long-term operation and accurate detection.[2] The third group includes minimally invasive sensors that bridge the gap between these noninvasive and invasive modalities[12] by situating most of the sensor outside of the body, but inserting probes inside to sample the extracellular fluids. This gives the advantage of sampling inaccessible bodily fluids in a relatively noninvasive manner near the body surface.

2 | BIOINTERFACED SENSING METHODS AND APPROACHES

Most of the bio-interfaced sensors are based on electronic components; although some are based on optical transducers, all demonstrated with non-invasive (eg, wearables and color-changing contact lenses)[13] or minimally invasive (color-changing tattoos) bio-diagnostic applications.[14] In essence, the transducer converts the targeted stimuli into a signal that can be measured—usually either an electric or a colorimetric signal. Colorimetric sensors are made from materials that change their color when exposed to certain stimuli. This limits them to noninvasive or minimally invasive applications, where the colorimetric material can be clearly seen, or to nonpoint-of-care applications, in which the stimuli have to be extracted first from the body and then exposed to the sensors. Electronic transducers are more common and can either be a resistor-, capacitor-, or transistor-based sensors. Resistor-based sensors change their resistivity and/or dimensions (ie, length or cross-section) on interaction with the targeted stimuli. Capacitor-based sensors change their capacitance on exposure to the targeted stimuli, either by changing the distance between the electrodes or changing the dielectric constant of the sandwiched dielectric. Transistor-based sensors combine features equivalent to the resistor- and capacitor-based sensors. Indeed, on exposure to the targeted stimuli, the measurable changes in source-drain current can provide a wide variety of simultaneous sensing parameters including threshold voltage, carrier mobility, drain-source current at a given gate voltage, and more.

For biodiagnostic applications, the biointerfaced sensors can target physical and/or (bio)chemical signals. Physical signals mainly include temperature and force-related parameters (pressure, strain, shear, etc.). Temperature is considered a primary index as it is a significant indicator of many health conditions,[15] which tends to affect all other sensors. Electromagnetic waves are also signals of interest, especially with the neural system, where the interaction between different cells/regions occurs electrically. On the other hand, chemical signals are wide and varied throughout the human body; this includes ions (Cl−, K+, Ca2+, etc.), volatile organic compounds (acetone, acetic acid, etc.), and small and large biological molecules (glucose, cortisol, proteins, etc.).

3 | DESIGN CONCEPTS

Unlike traditional sensors, a bio-interfaced sensor’s performance is not solely determined by the sensor’s physical sensing capabilities (sensitivity and detection limit). Instead, the chemistry and the biomechanics of the sensor’s interface with the surrounding bio-environment are also crucial for proper sensor function.

Generally speaking, noninvasive biointerfaced sensors are not associated with a danger of triggering a FBR. At worst, a poorly managed biointerface can irritate the attached tissue (skin or eye).[16] For invasive sensors, the sensor-tissue interface dictates the surrounding tissue’s response. If this interface is not carefully treated, a FBR may occur and violently reject the implanted sensor. Surrounding cells release reactive oxygen species and degenerative enzymes that create an acidic environment around the implant. Finally, fibrous tissue encapsulates the implanted device, isolating it from the body’s environment. This reaction is undesirable for two main reasons: first, as the FBR changes the surrounding biological environment of the implant, the measurements acquired by the device no longer represent the native bioenvironment. Second, some devices cannot withstand the FBR and ultimately fail.[18]

Minimally invasive sensors are usually exposed to extracellular fluids, at least partially. Extracellular fluids are rich in proteins and small cells, which can be adsorbed onto the sensor’s surface and cause fouling. If not carefully treated, the sensor’s interface can get “clogged” with biological matter, impairing its function and possibly causing infection.[17] Overall, minimally invasive sensors can be thought of as a compromise between invasive and noninvasive sensors. As such, we will not treat these sensors directly in the current review, as they are, in essence, a combination of the invasive and noninvasive sensors.
Research has mainly focused on two approaches to avoid undesired FBR: active coatings and material matching. Active coatings aim to stop FBR by the slow-release of anti-inflammatory drugs, enzymatic scavengers, and other agents - resulting in the effective triggering and subsequent subduction of a FBR. Under these conditions, the sensor can continue to function. Therefore, this approach is mostly useful for bioresorbable implanted sensors, or used in conjunction with the material matching approach (discussed below) for chronic implants. Farah et al. have demonstrated the long-term controlled release of anti-inflammatory compounds by developing compact crystals that can be attached to implantable devices. These formulations suppressed FBR in both rodents and nonhuman primates for over 1.3 years and 6 months, respectively. They also inhibited fibrosis across multiple implant sites—subcutaneous, intraperitoneal, and intramuscular. In particular, incorporating GW2580—a colony-stimulating factor 1-receptor inhibitor—into a range of devices, including human islet microencapsulation systems, electrode-based continuous glucose-sensing monitors, and muscle-stimulating devices, inhibited fibrosis and allowed extended function.

Meanwhile, to avoid triggering the FBR, there is a need for careful selection of the materials composing the bio-interfaced sensors while taking into account three primary considerations: surface chemistry (biocompatibility), structure (topology, texture, device shape, device size), and mechanical properties (bending and elastic moduli, stiffness, etc.). The operation time of a proposed device is another important factor to consider in the design and fabrication stage. While bioresorbable sensors are favorable in some applications, highly stable and durable sensors are required in others. Traditionally, this requirement concerns mainly implantable sensors. The primary trade-off between these two approaches is the limited variety of bioresorbable materials, whereas the main advantage is the reduced risk of additional resections to remove the devices. In such applications, the selection criteria rely on the ease of implantation and required duration time of the implant. In cases where the implant has to operate for an extended period (e.g., several years), and the implant location is hard to reach by surgery, highly stable and durable sensors are generally favorable. Meanwhile, in applications in which the implantation site requires surgery and the operation time is limited, biodegradable implants are preferable. In cases where the implantation site is accessible, other considerations are needed to decide on the optimal approach.

The design of bio-interfaced sensors will highly benefit from advances in the development of new functional materials. Biomimicry is an exciting route in this area where inspiration from the tissue of interest can guide the development of suitable bio-interfaced sensors. So far, multiple “natural” properties have been integrated into soft sensors, including self-healing, biocompatibility, self-cleaning, and self-monitoring. Seeking more combinations of such desirable functional, chemical and mechanical properties can provide solutions to intricate problems in the field of bio-interfaced sensors.

### 3.1 Surface chemistry and biology

The surface chemistry at the sensor’s interface with the biological environment should be biocompatible, that is, not carcinogenic, toxic, or allergenic. For noninvasive biointerfaced sensors, the compatibility of the surface chemistry is relatively simple because there is no danger of triggering FBR. In these cases, the surface chemistry just needs to be inert and not irritating to the skin. It is also important not to allow interfacial shearing, which can cause skin irritation and discomfort. An excellent example of this was recently reported by Zhang et al., who used a mussel-inspired hydrogel with excellent skin adhesion (~5 KPa) for strain sensing. The device was fabricated using biocompatible hydrogels mixed with carbon nanotubes (CNTs), making it very soft along with excellent surface chemistry, allowing comfortable strain sensing (Figure 1A).

Biocompatibility concerns for tissue-interfaced sensors are more complicated than that of skin-interfaced sensors. The moment a foreign body is inserted into the intercellular matrix, proteins from the biological environment at the vicinity of the sensor adsorb onto its surface and signal to the immune system. Towards this issue, the surface chemistry needs to be designed to make the implanted sensor “stealthy” to evade the body’s immune system. Coatings with some materials, such as polyethylene glycol (PEG) or zwitterionic polymers, can effectively reduce or eliminate cell adhesion, thus preventing the immune system from identifying a foreign object. An excellent example of this has recently been demonstrated by Anderson et al., who developed a microneedle glucose sensor. By coating the invasive portion of the sensor with a zwitterionic polymer, they found both a remarkable decrease in measurement noise and body response (Figure 2A, top). Rogers et al. reported an attractive alternative for bioresorbable sensors, in which the sensor is coated with natural wax with dual functionality: it reduces FBR with good chemical matching, and it slows down the degradation rate of the device, allowing modulation of the devices’ functional lifetime.

For an implanted sensor to remain functional over time, it must also “communicate” with the surrounding tissue. Human bodies use signals in the form of integrin ligands...
and cytokines to interact with the immune system.\[31,32\] To ingrain these cues into the surface chemistry, “receivers” from external cell membranes (ie, integrin ligands and cytokines) have to be attached to the sensor’s surface according to a well-defined distribution and/or patterns. An upgraded strategy of this direction relies on the so-called “biohybrid systems,” viz. electronic devices that use a biologically active intermediate layer between the tissue and the device surface. Once implanted, the pregrown cells integrate into the host tissue, forming a bridge between the electronics and the tissue.\[37\] A stable cell-tissue interface relies on an appropriate selection of the cells to be implanted, as poor choices may lead to an immune response similar to a graft rejection. Lessons learned from the long clinical history of cell transplants can be applied to optimize biohybrid sensing electronics. An excellent example of this was reported by Dvir et al.,\[38\] who developed integrated soft electrodes for electrical activity sensing of cardiac cells, achieving good biological signaling with the immune system. (Figure 2A, bottom).

### 3.2 Mechanical properties

For noninvasive sensors, incompatible material modulus might cause irritation and/or results in problems in sensor adhesion. Recent trends in this field aim to develop highly conformal and seamless sensors, which can operate without disrupting the user.\[39,40\] These design concepts have mainly focused on selecting the right mechanical properties and the design of ultrathin devices, while utilizing careful interface engineering. Wearable mesh electronics,\[41\] epidermal electronics,\[42\] and skin tattoos\[40\] are among the examples reported in the literature. Such considerations are especially crucial in neonatal care, where mechanical matching is much more important. Rogers et al.\[29\] considered the mechanical
strain distribution at the skin interface, and have even simulated it numerically (Figure 1B). Their simulations determined that up to 20% strain, the interfacial forces are below the thresholds for sensory perception. Their device’s mechanical characteristics ensure soft and irritation-free interfaces with the neonatal patient’s skin.

Mechanical matching plays a significant role with implanted sensor as implants are continuously exposed to micromotions inside biological tissues. Therefore, a mechanically mismatch interface will cause microinjuries to continually occur at the tissue interface, leading to stronger body response. The softer the sensor is, the less interfacial strain is applied at the interface, resulting in reduced risk of interfacial friction and ultimately improved biocompatibility. Bao et al. developed neural electrodes with comparable mechanical properties to nerve tissue. They introduced a method to prepare a highly conductive hydrogel encapsulated in a stretchable insulation material whose mechanical properties are tunable. They then created electrodes that are mechanically matched to nerve fibers and are orders-of-magnitude softer than previously described neural electrodes (Figure 2B). Their work shows conclusively that good material matching drastically reduced the body’s response to these sensors by epifluorescence and confocal microscopy. As the technology progresses, new methods for rapid prototyping of soft implantable electronics are being reported, which will lay the foundation for developing new material-matched sensors and can be used in future works as the interconnects/electrodes in a wide range of devices.

3.3 Device structure

Devices with identical surface chemistry and mechanical properties can have profoundly different biological responses with different device structures, ie, shape, size, and surface topology. This is because the
shape and size of a device change the distribution of mechanical forces at the tissue-sensor interface, as well as the tissue displacement volume incurred by its presence (volume of displaced tissue, equal to the device volume for implanted devices). On the other hand, surface topography—especially on the micrometer scale—affects the force per unit area observed by an implant, implant-tissue adhesion, adhered cell elongation processes, and more.\[46, 51, 52\]

The biocompatibility of noninvasive sensors is less dependent on device size and shape if the sensor’s modulus is smaller than that of the underlying tissue.\[53\] In cases where the sensor is stiffer than the skin (ie, its modulus is greater than the skin or less stretchable), then the device area and the applied location may affect its biocompatibility. Compared with invasive sensors, the reason for this disparity is that noninvasive sensors are placed outside the body. Therefore, increasing the device volume does not change the tissue displacement volume (as no tissue is displaced to begin with). Nevertheless, the current trend is to deviate away from bulky wearable devices (eg, a smartwatch) towards seamless ultrathin and ultralight wearable sensing devices that can conformally attach to the skin without disrupting the daily activities of the user (Figure 1C). The biointerface surface topology can also determine the biocompatibility of the device, as it determines the degree of contact with the underlying tissue and its exposure to bodily fluids. Even when the sensor is noninvasive, it can be exposed to salty fluids (sweat, tears) and proteins (in ocular and dental sensors). Therefore, in applications that target long-term monitoring, engineering the surface topology might be necessary to repel unwanted biomaterial adsorption, and allowing better adhesion and a more intimate contact with the underlying tissue.

An excellent example of these principles is demonstrated in the new field of electronic tattoos—in which the wearable devices are so thin and soft that only when they are attached to an external substrate (target tissue or temporary substrate) can they operate properly. Wang et al.\[54\] developed an electronic tattoo capable of noninvasively monitoring both sweat and interstitial fluid (glucose and alcohol). The device itself was fabricated by screen printing. A reference electrode was fabricated from a conductive Ag-Ag/Cl ink and a working electrode from a Prussian Blue conductive-carbon ink on ultrasoft agarose hydrogel and PVA cryogels that come in direct contact with the skin. In another demonstration, Khatib et al.\[55\] described a self-healing tattoo, FET-based sensing platform, which can be attached to the skin with very high conformity, thereby allowing very efficient monitoring of physiological parameters such as temperature and humidity.

Another biocompatibility consideration for noninvasive sensors that could be critical for controlling allergy and body response is the “permeability” factor. In this endeavor, Someya et al.\[41\] developed breathable wearable electronic devices with high permeability that allow water and oxygen to flow from and into the skin. Using a nanomesh conductors’ porous structure with excellent water vapor permeability, significant suppression of skin irritation and reduced inflammation compared with conventional plastic and elastomer films with lower gas permeability was achieved. Similar, but more complicated trends, were followed with wearable eye contacts, where permeability is vital to keep the eye from being irritated.\[56, 57\] Interestingly, among the various wearable healthcare devices, smart contact lenses have attracted great commercial attention for health care applications.\[9\] The cornea’s surface uniquely presents a convenient and noninvasive interface to many physiological conditions.\[59\] The design of these devices is more complicated as it has to include an additional set of properties along with the standard sensing capabilities. For example, to prevent interference with vision, transparency of the device is essential. There are also additional permeability requirements where the contact lens must be permeable to many molecules including water and oxygen. Finally, a compact and miniaturized wireless design is required, which adds to the complexity of the whole system.\[9\] Because of these stringent device requirements, the development of eye-interfacing sensors for diagnostic applications is highly complicated and requires further research.

In the case of invasive tissue-interfaced sensors, the biological response is also affected by the interfacial forces applied by the sensor. The density (pressure) of these forces is determined by the implant’s shape, size, and surface microtopology (texture). Rounder shapes have greater biocompatibility, as acute angles have higher densities of interfacial forces. That is why higher collagen densities are generally seen at the edges of implanted electronic devices. For example, for rectangular devices, thicker encapsulation layers are near the corners of the device.\[49\] In terms of size, it was recently shown that spheres of 1.5 mm or greater in diameter are more biocompatible than their smaller counterparts.\[58\] However, most studies show that reducing the size of the implant reduces the FBR. Larger implants cause more tissue disruption during implantation and displace larger tissue volumes.\[46, 50\] There might also be an orientation effect relative to the skin surface; since most of the collagen fibers are oriented parallel with the skin surface, larger sensor dimensions perpendicular to the skin might cause more collagen displacement and, therefore, stronger FBR.\[46, 50\] However, more research is...
needed to determine the effect that implant orientation has on FBR.

The final consideration in the device structure is its microtopology. The biointerface microarchitecture needs to be correctly engineered to reduce cell and tissue adhesion to the implant surface, and the force per unit area observed by the implant.[46] Nonspecific adhesion of cells and tissue to the implant surface is the root cause of FBR.[51] Proper microstructure engineering can relieve this phenomenon by reducing cell adhesion to the biointerface and impeding cell spreading and elongation. Micron-scale isotropic elements arranged in a symmetric and regular pattern can physically block these processes.[51] In addition, certain microstructures cause direct physical interference to the establishment of focal adhesion and maturation during cell spreading. Microtopography patterns may be composed of pillars, wells, pyramids, inverted pyramids, and more.[46, 51] The design rationale for these geometries is to physically block the process of spreading and elongation of adhered cells.[51] By making the surface of the implant noncontinuous on the same length scale that these processes occur, they are effectively stifled. Uniform and isotropic patterning help to prevent preferential elongation in a particular direction, thereby improving overall performance.[51] A few different design strategies are available. In cases where the interfaced material has an established lithography protocol, it is possible to design any of these topographies using optical lithography.[46, 51, 59] If lithography is problematic, it is sometimes possible to coat the biointerface with an intermediate material that is compatible with lithography processes. In cases where such processes are detrimental to the sensor function, porous coating materials make an attractive possibility.[46, 52] An obvious exception to these considerations is biohybrid devices, in which the cell implantation deters nonspecific protein adhesion at the surface, thereby promoting specific protein adhesion and ultimately tissue integration. An excellent example of the effect of the sensor shape and size on the body response was reported by Leiber et al.[44] By mimicking the native neuronal structure, they developed neural interfaces that were similar in shape and size to single neurons. These devices formed highly stable structural and functional interfaces with the surrounding bioenvironment (Figure 2C).

As discussed in the text above, biocompatibility and the corresponding device considerations change radically with different tissues. Table 1 summarizes the different properties that are desirable for a device from a biocompatibility point of view. As not all of the different biocompatibility considerations have been demonstrated for all tissue types for biointerfaced sensors, some of these are taken from the tissue implant/scaffold engineering field. The table basically gives the general guidelines for achieving optimal biocompatibility for future research in biointerfaced sensors.

## 4 | BIODIAGNOSTICS AND BODY MONITORING

The coronavirus disease 2019 (COVID-19) pandemic has emphasized the urgent need to enhance and develop the existing medical and healthcare systems. Combined with the many other infectious and chronic diseases (eg, Alzheimer’s, cancer, heart disease) that remain a major global health issue, there is enormous pressure to develop new biodiagnostic tools. One effective way to mitigate these challenges is by improving early diagnosis and body monitoring. The currently most reliable diagnostic methods include radiology (eg, X-ray, MRI, CT), in-vitro medical assay (eg, urine, blood, stool), and pathological and clinical microbiological examinations (eg, histology and cell cultures). However, most of these diagnostic methods are complex and require much analytical equipment. Therefore, they can only be analyzed at centralized hospitals and laboratories, and are relatively slow, expensive, and require medical professionals.[4] For these reasons, biointerfaced sensors could provide rapid, simple, cheap, and continuous biodiagnostics, without a need to visit healthcare facilities, thus, reducing both time and cost.[2]

Using biointerfaced sensors for body monitoring and diagnosis relies on the analysis of physical (eg, pressure and temperature) and/or chemical (eg, pH and biomolecules) signals generated by the body (Table 2). Therefore, sensors have been applied for monitoring different physiological parameters, such as vital signs (eg, heartbeat, respiration rate, blood oxygen, and temperature) and biomarkers (eg, glucose, acetone, and ions) found in sweat, tears, skin odor, etc.[77, 78] By continuous or frequent detection of the level of physical/chemical/biological signals, sensors can provide comprehensive feedback on the state of human health. Particular attention in this area has been given to body fluids, including blood, urine, sweat, breath, saliva, interstitial fluid, seminal fluid, nipple aspirate fluid, tears, stool, and cerebrospinal fluid, as they are highly indicative of diseases and body conditions.[4]

### 4.1 | Neurological disorders

The diagnosis and understanding of neurological disorders and brain diseases can be achieved using a range of biological and physiological indicators in different parts of the body, mainly the brain. Though noninvasive diagnostics are possible, high-resolution information is often collected using invasive electrical and chemical measurements.[117]
### TABLE 1 Implementation options for the different biocompatibility considerations for different tissue types

| Tissue                  | Surface chemistry                        | Mechanical properties | Device shape | Implant geometry |
|-------------------------|------------------------------------------|-----------------------|--------------|-----------------|
|                         |                                          | Young’s modulus [kPa] | Strain range | Surface topology | Implant geometry |
| Cardiac                 | Polyethylene glycol (PEG) [60]           | 10–15 [63]            | 10–20%, every 5–25 ms | Pores [64]       | –                |
|                         | Hyaluronic acid (HA) and dopamine (PDA) [61] | –                     | –            | –                | –                |
|                         | Zwitterionic [62]                         | –                     | –            | –                | –                |
| Gastrointestinal tract  | Just inert and durable [65]              | 1-1000 [66, 67]       | Every 20-145 ms | –                | –                |
| Central nervous system  | PEG hydrogels (not brush) [68]           | 1–4 [61]              | –            | –                | Microwires [44]  |
| Liver and kidney        | Polyethylene glycol, zwitterionic polymers [31, 62] | 8–12 [63]            | –            | Micropillars, microwells, micropump [46] | Small and round, small dimensions parallel to the skin [46] |
| Skin                    | Innert, eg. PDMS, vinylsiloxane [69]     | ~85 [70]              | 100% [71]    | Micropillars, microwells, microbumps, microsucker [69] | Ultrathin and flat [72] |
| Muscle                  | Polyethylene glycol, zwitterionic polymers [31, 62] | 10–20 [61]           | –            | Micropillars, microwells, micropump [46] | Small and round, small dimensions parallel to the skin [46] |
| Tendon                  | Polyethylene glycol, zwitterionic polymers [31, 62] | 1300-170 [63]        | 2–5% [71]    | Micropillars, microwells, microbump, pores [9, 46] | –                |
| Cornea                  | Zwitterionic polymers [74]               | ~29 [70]              | –            | –                | Smooth [78]      |
| Blood vessels           | Polyethylene glycol, zwitterionic polymers [31, 62] | ~125 [70]            | 10-20% [76]  | Micropillars, microwells, micropump [46] | Small and round, small dimensions parallel to the skin [46] |
| Fat                     | Polyethylene glycol, zwitterionic polymers [31, 62] | 0.5–3 [63]           | –            | Micropillars, microwells, micropump [46] | –                |

Electrical communication signals between neurons, which eventually determine the brain’s state, can be sensed with miniaturized recording electrodes located within hundreds of micrometers from the cell [118]. Due to neuronal organization into layers, higher amplitude electrical signals are generated by a large population of neurons. Such signals undergo spatial summation and can be detected at much greater distance from the neurons as oscillatory patterns and waveforms with frequencies ranging between 0.5 and 500 Hz [119]. The data’s spatial and temporal resolution depend on whether it is recorded from the surface of the scalp, brain, or within brain tissue. Interestingly, these signals are highly related to brain activities and dysfunctions.

Noninvasive methods of recording brain activity are frequently used in clinical neurology and include electroencephalography (EEG) and magnetoencephalography (MEG). In the case of EEG, electrodes are placed at standardized positions on the surface of the scalp to detect fluctuations in voltage in the range of 10–100 μV [117]. EEG is a powerful tool for acquiring real-time information about brain function. The most common EEG diagnostic applications are in epilepsy, altered states of consciousness and brain lesions [120]. One interesting form of EEG is the intracranial EEG (iEEG) that involves placing electrodes on the cortical surface in the form of grid arrays or strips, and/or inserting electrodes in the form of a rigid shank with multiple contacts directly into brain tissue. iEEG has the benefit of enhanced spatiotemporal resolution [121]. MEG acquires the magnetic rather than electric signals generated by the population activity of neurons in the brain. Because the magnetic field is orthogonal to the electric field, MEG is better at detecting signals arising from
TABLE 2  Representative examples of diseases and their related measurable signals, where the integration of biointerfaced sensors for biodiagnostics is highly promising

| Field          | Disease/condition | Electrophysiology                                      | Physical/chemical signal                      | Biomarkers                                                                 |
|---------------|-------------------|--------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------|
| Neurology     | Alzheimer's       | EEG (slower) [79]                                      | VOCs [80]                                     | t-tau, p-tau181, Aβ42, and Aβ40 [81]                                        |
|               | Epilepsy          | EEG (pathological high-frequency oscillations) [82]    | Oxidative stress related markers [83] VOCs [84] | Multiple (eg, increased concentration of hsa-miR-106b-5p) [85]             |
|               | Parkinson's       | EEG (synchronized oscillation in the beta band) [79]  | VOCs [86]                                     | Dopamine [87]                                                              |
| Cardiology    | Myocardial infarction | Electrocardiography (ST elevation or depression, T-wave inversion) [88] | Irregular heartbeats, abnormalities in blood pressure [89] | Troponin [89, 91] B-type natriuretic peptide (BNP), [91] N-terminal pro BNP (NT-pro BNP), [92] high sensitivity CRP (HS-CRP) [91] |
|               | Atrial fibrillation | Electrocardiography (no P waves, irregular RR intervals) [90] | Irregular heartbeats, [94] diastolic and systolic blood pressure [91] | BNP, NT-proBNP, CRP [86]                                                  |
| Cancer        | Melanoma          | ——                                                     | pH, pressure, temperature, O2 (local) [97]     | Many (eg, Human Melanoma Black-45)                                          |
|               | Brain tumor       | EEG [99]                                               | pH, pressure, temperature, O2 (local) [97]     | Many (MIC-1 GDF15 in glioblastoma)                                          |
| Diabetes      | Diabetes          | ——                                                     | VOC (eg, acetone) [90]                         | Glucose/insulin                                                            |
| Infectious    | TB                | ——                                                     | Exhaled breath VOCs [102, 103]                  | MTB genomic DNA [104] ESAT-6 protein [105]                                  |
| disease       | Flu               | ——                                                     | Exhaled breath VOCs [106]                      | DNA aptamer [107] Viral RNA [108] Neuraminidase [108] Hemagglutinin [108] |
|               | Malaria           | ——                                                     | Exhaled breath VOCs [109]                      | Enzymes [1, 10], P/HRP-II, P/LDH, P/ALD, P/HGPRT, P/GluDH Products [101]: hemoglobin |
|               | COVID 19          | ——                                                     | Exhaled breath VOCs [111-115]                  | Viral RNA [114] Antibodies and inflammatory biomarker [115, 116]          |

fields tangential to the scalp. It is also less attenuated by the barriers between the neurons and the recording electrodes (eg, cerebrospinal fluid, dura, skull, and subcutaneous tissue). [122] Clinically, MEG has been mainly used to supplement and refine the localization of epileptic foci within the brain.

Electromyography is another biointerfaced based method for evaluating muscle functions. It involves the insertion of a concentric or monopolar needle through the skin and into a muscle to record muscle fiber action potentials that might indicate the existence of neurological diseases in motor neurons, motor nerves, or muscle. [123] This can typically identify the disease type, narrowing further investigations to reach a specific diagnosis. However, the main drawback is the need for skin penetration. Nerve function can also be analyzed through electrodes placed on the skin to elicit action potentials, a test called nerve conduction study (NCS). [124] NCS provides important diagnostic information when patients experience motor and sensory symptoms, identifying loss of nerve fibers or impaired ability to conduct action potentials. When a disease process affecting the nerves is diagnosed, such as a demyelinating condition or toxic exposure, NCS can also be used to track recovery over time. [125]

The aforementioned recording methods have been in use within several parts of the human nervous system, and have greatly contributed to advancing our understanding of the nervous system. However, the devices used have very
different physical and chemical properties compared to the tissue of interest, triggering a FBR inside the body and/or allergic response on the skin—which prevents their long-time operation. Therefore, many groups have explored new measurement tools, including neuron-like and grid/mesh electronics for the brain/nervous system, and imperceptible and seamless sensors/electrodes for the skin.\textsuperscript{[126]} This showed a clear transfer from bulky metal recording electrodes to nanostructured organic-inorganic hybrid micro-/nanostructured systems and polymeric formulations including composites and hydrogels.\textsuperscript{[126, 127]} Current trends seek to make these sensing devices as similar as possible to the biological tissues at the interface. However, even though soft materials seem like a great candidate for minimizing the mismatch with biological tissues, they usually fail to meet the requirements of chronic applications. Therefore, inorganic materials can be the optimal solution for long-lasting applications. For example, the state-of-the-art recording system, called “Neural Matrix,” is based on a flexible and multiplexed electrode array that provides stable in-vivo neural recordings in rodents and nonhuman primates.\textsuperscript{[128]} Neural Matrix lasts over a year and samples a centimeter-scale brain region using over 1000 channels. The long-lasting encapsulation can potentially last at least 6 years. These results demonstrate possible solutions to several critical challenges faced by all active implantable electronics in the body.

Besides electrical activity, chemical and biological signaling in the human nervous system is essential. Interneuron communication consists of the transmission/reception of unique chemical compounds, neurotransmitters, at synapses. These materials can be monitored using neurochemical sensing probes that establish a valuable diagnostic and therapeutic tool. The monitoring of neurochemicals can be used to study neurodegenerative diseases characterized by deficiencies in neurotransmitter signaling.\textsuperscript{[129]} Even though the integration of sensors for monitoring and diagnosing neurological disease has been scarcely shown, it seems a promising direction for the future of biointerfaced sensors. An interesting example focused on the chronic detection of dopamine, an important neurotransmitter governing behavior that has been heavily implicated in a large range of neural disorders including Parkinson’s disease, depression, and related mood and movement disorders. Using a carbon fiber sensor with fast-scan cyclic voltammetry, dopamine release could be measured from multiple sites in nonhuman primate striatum.\textsuperscript{[130]} In this specific case, reduction in implant size was critical to ensure minimal brain response and stable long-term monitoring. These findings demonstrate the long-term feasibility and reproducibility of neurochemical measurements, strengthening their potential translation to human biodiagnostics.

### 4.2 Cardiac irregularities

A variety of chest patches have been developed for ambulatory and noninvasive cardiac monitoring. For example, the FDA-approved adhesive Zio Patch by iRhythm Technologies (San Francisco, CA) provides prolonged detection and diagnosis of irregular heart rhythm including atrial fibrillation (AF). Zio Patch overcomes the rigidity of the conventional Holter monitor by implementing a wearable device capable of scanning and recording electrocardiographic signals for two weeks and wirelessly transmitting the acquired data.\textsuperscript{[131]} Other wearable, bendable, and soft electronics have been developed for real-time sensing of vital and physiological cardiac parameters including continuous and real-time electrocardiography (ECG) and flexible heartbeat sensors.\textsuperscript{[132]} For example, BioStamp nPoint (MCI0 Inc., USA), a soft, adhesive and flexible bandage-like device, can provide real-time streaming of ECG, heart rate, and respiration signals.\textsuperscript{[133]}

Further developments include the fabrication of non-rigid, epidermal, and skin-conformal bioelectronics. Lu et al.\textsuperscript{[134]} reported on a stretchable and ultrathin electronic chest tattoo based on piezoelectric sensors designed for synchronous and simultaneous measurement of seismocardiography and ECG signals. The reported device can estimate heart vibrations and systolic time intervals correlated to the systolic and diastolic blood pressure. Bao et al.\textsuperscript{[135]} demonstrated a self-healable and stretchable platform that integrated ECG and strain sensors with a light-emitting capacitor array. The ECG and strain sensors wirelessly transmitted their measurements to the light-emitting capacitor array that displayed the signals, enabling real-time monitoring and an intuitive communication pathway.

Integration of stretchable and biocompatible electronics that suit the myocardium’s deformable and stretchable nature have also been reported. These devices are designed in various patterns, including sleeves, thin films, or meshes that conform to heart tissue and the cardiac contraction. Kim et al.\textsuperscript{[136]} have demonstrated a stretchable, biocompatible, and highly conductive 2D cardiac mesh composed of conductive nanocomposites and an elastomeric substrate. This mesh could detect heart contractions and mechanical strain distribution. Rogers et al.\textsuperscript{[137]} integrated electronics with catheters along with biocompatible soft interfaces for mapping and monitoring cardiac function during minimally invasive surgery. Bao et al.\textsuperscript{[138]} described an innovative sensing platform allowing electrophysiological mapping of chronic AF at high throughput and high resolution. This platform addressed the limitations of the current electrophysiological tools, specifically the low spatial resolution and the electromechanical signal uncoupling of the heart during contractions. The device was proven
in a series of tests on rabbit and porcine models to have robust and intimate tissue coupling, while maintaining its chemical, mechanical, and electrical properties during the cardiac cycle. The array recorded epicardial atrial signals and reliably identified clinically relevant electrophysiological heterogeneity in the pathologic state of pacing-induced chronic AF.\textsuperscript{138}

Electronic implants have also been integrated with tissue engineering and cardiac regeneration, merging sensing and mapping capabilities with cardiac recovery and rehabilitation. Improved cardiac regeneration has recently been achieved after heart failure by using a conductive mesh to detect electrical signals and diastolic heart murmur distinctive of heart failure and postmyocardial infarction. The mesh could also provide cardiac pacing and electrical shocks for restoring normal heart function and effectively improving the recovery of the cardiac tissue.\textsuperscript{139}

\subsection{Cancer}

Cancer is a dreadful disease with a high mortality rate, becoming increasingly more prevalent worldwide. Cancerous tissue generates multiple characteristic biological, chemical, and physical signals.\textsuperscript{140} These signals can be detected via the biointerfaced sensors for early diagnosis and treatment monitoring. In particular, electrochemical signals are strong candidates for enabling ultrasensitive, highly selective, low-cost, and quick cancer theragnostics.\textsuperscript{141} Measurement and analysis of cancers using electrochemical biosensors at the molecular, organellar, and cellular levels have been comprehensively discussed in the literature.\textsuperscript{141, 142}

Electrochemical sensors have mainly targeted biological compounds that are most upregulated in cancer. However, almost all of the currently targeted compounds are also expressed in normal cell populations, leading to difficulties in obtaining high detection selectivity. In addition, biologically, cancers tend to have a high degree of variance due to their heterogeneous nature.\textsuperscript{143} The dynamic process of tumor development results in a major change from the natural microenvironment, leading to profiles of hypoxia and acidity, increased thermal/electrical conductivity, and different mechanical forces and properties.\textsuperscript{143} Therefore, it is promising to consider the underlying tumor microenvironment in developing more effective and selective cancer biodiagnostics. In such cases, the intimate interface with the tumor is crucial for collecting reliable data.

Future work is expected to integrate more cancer biodiagnostic capabilities into biointerfaced devices for early diagnosis and continuous monitoring of the tumor conditions. Advanced implantable devices might be developed to monitor tumor regrowth after resection, where early reintervention might be needed.\textsuperscript{145} Wearable devices that have a continuous interface with the human body can potentially detect and follow cancerous markers through the body’s external surfaces.

\subsection{Infectious diseases}

Infectious diseases are caused by many microorganisms, such as bacteria, viruses, fungi, and parasites.\textsuperscript{144} Disease transmission can occur by direct contact with people, animals, environment (water, soil), or insect bites. The distribution of these diseases is strongly correlated to categorization of economic income. Most deaths in low-to-middle-income countries are associated with infectious diseases including tuberculosis, malaria, lower respiratory infections, and many others.\textsuperscript{145} Rapid detection of infectious diseases, especially before symptoms appear, is critical for individual and public health as it reduces disease transmission, and establishes surveillance and disease control. Precise diagnosis is crucial in selecting a suitable treatment. However, most of disease symptoms are broadly general, making it complicated to diagnose without molecular testing.

The majority of currently developed sensors for the rapid detection of communicable diseases are based on immunoassay-immunosensor-based technologies.\textsuperscript{108, 113, 116, 146} These include, but are not limited to, electrochemical, optical, piezoelectric, colorimetric, and magnetic platforms to detect specifically targeted analytes. The primary sample sources are swabs and blood samples. Another research field is based on nonspecific detection aided by machine learning to target disease analytes from exhaled breath, saliva, and skin.\textsuperscript{102, 106} While current sensing techniques have achieved considerable progress, there is still an urgent demand for rapid and straightforward methods. Only a minor portion of the developed technologies are portable and can serve as a potential point of care (POC)-based sensor test.\textsuperscript{103, 107, 112, 113, 116, 147-149} Furthermore, none of these reported systems is a specific personal wearable device for communicable diseases.

A portable handheld platform based on giant magnetoresistive\textsuperscript{149} and graphene-based sensors\textsuperscript{148} have been described for the detection of influenza A virus and malaria from nasal swab and saliva, respectively. After further development and miniaturization, POC devices can be integrated into a wearable device, for example, a mask or nose cannula. Other examples include Malaria detection from blood, either by patches with microneedles for detection of specific biomarkers in the blood (eg, PfHRP2 ) based on label-free immunoassay\textsuperscript{150} or by a
transdermal optical excitation and acoustic detection of vapor nanobubbles around malaria-infected cells.\cite{lee2015}

These platforms allow laboratory testing to be performed outside. Another example is COVID-19 detection by a portable multiplexed immunosensor platform using blood and saliva samples.\cite{kim2020}

Based on disposable graphene electrodes, this device is sensitive to a wide range of viral proteins, antibodies, and an inflammatory biomarker. The device has a wireless connection to an application that gives it the potential to become a POC device for disease detection and monitoring.

In addition, the monitoring of nonspecific symptoms, such as temperature, heart rate, and coughing, can be accomplished by wearable devices and serve as additional parameters in modeling disease progression from the prospective of an individual's unique baseline.\cite{lee2021}

Future integration of several sensing platforms, including specific and nonspecific analyte detection, such as temperature and cough monitoring within skin patches, dental implants or masks, may offer a significant breakthrough in detecting and/or discriminating some infectious diseases.

This technological leap's challenges include two almost conflicting aspects: miniaturization while remaining affordable so that such developments are suitable for use in low- to middle-income countries. Such devices pave the way for the development of diagnostic and treatment monitoring tools to reduce the biohazard risks associated with specimen collection and test accessibility in rural areas.

4.5 Diabetes

Diabetes is one of the most prevalent chronic diseases, causing unregulated blood glucose levels.\cite{worldhealthorganization2020}

Patients with diabetes are advised to check their blood glucose level daily and take periodic insulin injections.\cite{american糖尿病学会2020}

As of now, wearable devices have taken several forms for glucose monitoring, including textile, patches and tattoos, and were shown on different parts of the body including chest, arm, eyes and mouth.\cite{zohar2020}

Several interesting examples of glucose monitoring devices can be found both in the academic and industrial sectors. One example is a wearable artificial pancreas for glucose monitoring and regulation. In this device, the sensing region is combined with an insulin-releasing system to provide a closed-loop feedback.\cite{merzer2020}

Another example, developed by Google/Verily Life Sciences in collaboration with Novartis, relies on the design of a smart contact lens to measure blood sugar levels.\cite{zohar2020}

The design and integration of wireless power transfer circuits, therapy, and display pixels to visualize sensing signals in real time with lens-based biointerfaced sensors has also been reported.\cite{lee2021,worldhealthorganization2020}

Lee et al.\cite{lee2021} have recently introduced a disposable wearable device that combines both glucose monitoring and a multistage transdermal drug-delivery module. In this example, careful multilayer patch design and miniaturization of sensors increased sweat collection and sensing efficiency. The multimodal glucose sensing, as well as its real-time correction based on pH, temperature, and humidity measurements, maximized the accuracy of sensing. Drugs for transdermal feedback therapy were loaded onto two different temperature-responsive phase change nanoparticles, which were embedded in hyaluronic acid hydrogel microneedles, also coated with phasechange materials. This enabled multistage, spatially patterned, and precisely controlled drug release in response to the patient's glucose level. This example provides a novel closed-loop solution for the noninvasive sweat-based management of diabetes mellitus.

5 SUMMARY AND OUTLOOK

The massive increase in the diversity of biointerfaced sensing platforms in recent years proves the significance of this research, but future work should take slightly different routes to solve the present challenges. These challenges are not only confined to the biological/physiological aspects, but relate to general limitations in the field of sensors. Calibration and signal interference, signal transfer methods, power sources, stability, accuracy selectivity, and compatibility, are among the main challenges faced in the field of soft sensors. Despite the promises from wearable and implantable sensors, they still lack the accuracy and sensitivity required for robust disease detection and diagnosis. This is mainly because of their inevitable exposure to multiple physical, chemical, and biological interfering signals. To interrogate this complexity of signals, careful hardware and software developments are required. Strategies to address this issue are based on using multiresponsive materials or integrating multiple types of sensors. This provides more information about the environment, and improves discrimination of signals, especially when the sensors are well designed to have high selectivity. On the other side, the use of advanced software and machine learning is an essential and complementary part of interpreting complex signals.

Currently, there are many examples of biointerfaced sensors that target chemical, physical, and biological signals generated by the body, but very few examples have shown successful diagnosis. On the other hand, successful examples of diagnosis using simple portable sensors have been
shown; in many cases, the system can be potentially turned into a biointerfaced sensor. For example, densely aligned CNTs were proposed to target Alzheimer’s disease via multiplexed sensing of biomarkers (t-tau, p-tau181, Aβ42, and Aβ40) in human plasma.\[^{81}\] Although this approach was based on an indirect interface with the human body, the concept of the sensor design, data collection, and interpretation are possible future research directions. Translating such strategies to biointerfaced sensors will be beneficial and hopefully lead to the introduction of more devices for disease diagnosis.

In-vitro use of biointerfaced sensors provides a cheap method for improving our understanding of many biological issues including the compatibility, stability of devices, and biodiagnostic capabilities. More interestingly, the use of biointerfaced sensors with organoids—small organs derived from differentiating stem cells in vitro—is expected to attract more attention. For example, organoids developing a neural circuitry reminiscent of their in-vivo counterparts have begun to emerge as an in-vitro model.\[^{158}\] This offers a complementary approach that helps to optimize the use of biointerfaced sensors for biodiagnostics. We strongly encourage researchers to expand this direction by finding advanced diagnosis methods using tissue cultures, which could lead on to studies with humans and animal models.

Following the recent interest in closed-loop systems, where precise and personalized modulation methods are determined based on the analysis of desirable targeted signals,\[^{159}\] we expect to see an increasing demand for the development of biointerfaced sensing components. Herein, we discussed the main target of such technologies, that is, biodiagnostics. However, these novel tools can be harnessed to improve our understanding in many basic physical, chemical, and biological processes occurring in the human body.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1. A. A. Mathew, A. Chandrasekhar, S. Vivekanandan, Nano Energy 2020, 105566.
2. D. Rodrigues, A. I. Barbosa, R. Rebello, I. K. Kwon, R. L. Reis, V. M. Correlo, Biosensors 2020, 10, 79.
3. T. R. Ray, J. Choi, A. J. Bandodkar, S. Krishnan, P. Gutruf, L. Tian, R. Ghaffari, J. A. Rogers, Chem. Rev. 2019, 119, 5461.
4. Y. Y. Broza, Z. Zhou, M. Yuan, D. Qu, Y. Zheng, R. Vishkin, M. Khatib, W. Wu, H. Haick, Chem. Rev. 2019, 119, 17161.
5. R. Gaetani, E. A. Zizzi, M. A. Deriu, U. Morbiducci, M. Pesce, E. Messina, Frontiers in Cell and Developmental Biology 2020, 8, 334.
6. a) C. Wang, K. Xia, Y. Zhang, D. L. Kaplan, Acc. Chem. Res. 2019, 52, 2916; b) S. Mondal, N. Zehra, A. Choudhury, P. K. Iyer, ACS Applied Bio Materials 2020; c) C. Cui, Q. Fu, L. Meng, S. Hao, R. Dai, J. Yang, ACS Appl. Bio Mater. 2020, 4, 85; d) R. Moreddu, D. Vigolo, A. K. Yetisen, Adv. Healthc. Mater. 2019, 8, 1900368.
7. M. Barita, H. Y. Y. Nyein, A. Javey, Nat. Electron. 2018, 1, 160.
8. M. S. Mannoor, H. Tao, J. D. Clayton, A. Sengupta, D. L. Kaplan, R. R. Naik, N. Verma, F. G. Omenetto, M. C. McAlpine, Nat. Commun. 2012, 3, 763.
9. N. M. Farandos, A. K. Yetisen, M. J. Monteiro, C. R. Lowe, S. H. Yun, Adv. Healthc. Mater. 2015, 4, 792.
10. C. Steiger, A. Abramson, P. Nadeau, A. P. Chandrakasan, R. Langer, G. Traverso, Nat. Rev. Mater. 2019, 4, 83.
11. a) Y. Song, J. Min, W. Gao, ACS nano 2019, 13, 12280; b) G. Rong, S. R. Corrie, H. A. Clark, ACS sensors 2017, 2, 327.
12. a) H. Teymourian, M. Parrilla, J. R. Sempionatto, N. F. Montiel, A. Barfidokht, B. Van Echelpoel, K. De Wael, J. Wang, ACS sensors 2020, 5, 2679; b) K. Y. Goud, C. Moonla, R. K. Mishra, C. Yu, R. Narayan, I. Litvan, J. Wang, ACS sensors 2019, 4, 2196.
13. a) A. Koh, D. Kang, Y. Xue, S. Lee, R. M. Pielak, J. Kim, T. Hwang, S. Min, A. Banks, P. Bastien, M. C. Manco, L. Wang, K. R. Ammann, K.-I. Jang, P. Won, S. Han, R. Ghaffari, U. Paik, M. J. Slepián, G. Balooch, Y. Huang, J. A. Rogers, Sci. Transl. Med. 2016, 8, 366ra165; b) R. Moreddu, M. Elshefri, H. Butt, D. Vigolo, A. K. Yetisen, RSC. Adv. 2019, 9, 11433.
14. A. K. Yetisen, R. Moreddu, S. Seifi, N. Jiang, K. Vega, X. Dong, J. Dong, H. Butt, M. Jakobi, M. Elsner, A. W. Koch, Angew. Chem. 2019, 131, 10616.
15. X. Wang, Z. Liu, T. Zhang, Small 2017, 13, 1602790.
16. J. Heikenfeld, A. Jajack, J. Rogers, P. Gutruf, L. Tian, T. Pan, R. Li, M. Khine, J. Kim, J. Wang, J. Kim, Lab on a Chip 2018, 18, 217.
17. a) S. Sharma, E. Takagi, T. Cass, W. Tsugawa, K. Sode, Procedia technology 2017, 27, 208; b) P. Dardano, I. Rea, L. De Stefano, Current Opinion in Electrochemistry 2019, 17, 121.
18. L. Davenport Huyer, S. Pascual-Gil, Y. Wang, S. Mandla, B. Yee, M. Radisic, Adv. Funct. Mater. 2020, 30, 1909331.
19. C. Boehler, C. Kleber, N. Martini, Y. Xie, I. Dryg, T. Stieglitz, U. Hofmann, M. Asplund, Biomaterials 2017, 129, 176.
20. S. Farah, J. C. Doloff, P. Müller, A. Sadraei, H. J. Han, K. Olafson, K. Vyas, H. H. Tam, J. Hollister-Lock, P. S. Kowalski, M. Griffin, A. Meng, M. McAvoy, A. C. Graham, J. McGarrigle, J. Oberholzer, G. C. Weir, D. L. Greiner, R. Langer, D. G. Anderson, Nat. Mater. 2019, 18, 892.
21. C. Mas-Moruno, B. Su, M. J. Dalby, Adv. Healthc. Mater. 2019, 8, 1801103.
22. G. D. Cha, D. Kang, J. Lee, D. H. Kim, Adv. Healthc. Mater. 2019, 8, 1801660.
23. a) C. E. Diesendruck, N. R. Sottos, J. S. Moore, S. R. White, Angew. Chem. Int. Ed. 2015, 54, 10428; b) M. Khatib, O. Zohar,
153. N. Cho, J. Shaw, S. Karuranga, Y. Huang, J. da Rocha Fernandes, A. Ohlrogge, B. Malanda, Diabetes Res. Clin. Pract. 2018, 138, 271.
154. D. Control, C. T. R. Group, N. Engl. J. Med. 1993, 329, 977.
155. a) D. Bruen, C. Delaney, L. Florea, D. Diamond, Sensors 2017, 17, 1866; b) A. J. Bandodkar, W. Jia, C. Yardmnci, X. Wang, J. Ramirez, J. Wang, Anal. Chem. 2015, 87, 394; c) J. Kim, A. S. Campbell, J. Wang, Talanta 2018, 177, 163.
156. J. Park, J. Kim, S.-Y. Kim, W. H. Cheong, J. Jang, Y.-G. Park, K. Na, Y.-T. Kim, J. H. Heo, C. Y. Lee, F. Bien, J.-U. Park, Sci. Adv. 2018, 4, eaap9841.
157. H. Lee, C. Song, Y. S. Hong, M. S. Kim, H. R. Cho, T. Kang, K. Shin, S. H. Choi, T. Hyeon, D.-H. Kim, Sci. Adv. 2017, 3, e1601314.
158. Q. Li, K. Nan, P. Le Floch, Z. Lin, H. Sheng, T. S. Blum, J. Liu, Nano Lett. 2019, 19, 5781.
159. a) C. M. Proctor, A. Slézia, A. Kaszas, A. Ghestem, I. Del Agua, A.-M. Pappa, C. Bernard, A. Williamson, G. G. Malliaras, Adv. 2018, 4, eaau1291; b) A. D. Mickle, S. M. Won, K. N. Noh, J. Yoon, K. W. Meacham, Y. Xue, L. A. McIlvried, B. A. Copits, V. K. Samineni, K. E. Crawford, D. H. Kim, P. Srivastava, B. H. Kim, S. Min, Y. Shiuan, Y. Yun, M. A. Payne, J. Zhang, H. Jang, Y. Li, H. H. Lai, Y. Huang, S.-I. Park, R. W. G. IV, J. A. Rogers, Nature 2019, 565, 361.

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