**2D Material Grounded Nanobiosensors: 2D (Diagnostic and Detection)**

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Nanobiosensors are devices that utilize a very small probe and any form of electrical, optical, or magnetic technology to detect and analyse a biochemical or biological process. With an increasing population today, nanobiosensors have become the broadly used electroanalytical tools for the timely detection of many infectious (dengue, hepatitis, tuberculosis, leukaemia, etc.) and other fatal diseases, such as prostate cancer, breast cancer, etc., at their early stage. Compared to classical or traditional analytical methods, nanobiosensors have significant benefits, including low detection limit, high selectivity and sensitivity, shorter analysis duration, easier portability, biocompatibility, and ease of miniaturization for on-site monitoring. Very similar to biosensors, nanobiosensors can also be classified in numerous ways, either depending on biological molecules, such as enzymes, antibodies, and aptamer, or by working principles, such as optical and electrochemical. Various nanobiosensors, such as cyclic voltametric, amperometric, impedimetric, etc., have been discussed for the timely monitoring of the infectious and fatal diseases at their early stage. Nanobiosensors performance and efficiency can be enhanced by using a variety of engineered nanostructures, which include nanotubes, nanoparticles, nanopores, self-adhesive monolayers, nanowires, and nanocomposites. Here, this mini review recaps the application of two-dimensional (2D) materials, especially graphitic carbon nitride (g-C3N4), graphene oxide, black phosphorous, and MXenes, for the construction of the nanobiosensors and their application for the diagnosis of various infectious diseases at very early stage.

**Keywords:**diagnosis; immunosensors; nano biodevices; nanobiosensors; nanomaterials; point of care; two dimensional nanomaterials.

**Introduction**

The revolution of life science and biotechnology in modern society has urged due to pandemic outbreak. Biotechnology includes genetic engineering [1-2], molecular biology [3], biochemistry [4], cell biology [5], embryology [6], immunology [7], and biosensing [8,9] system. The biosensing approach is one of the most important systems for health testing, epidemic control, and disease diagnosis in complex situations. The technique of biosensing has been developed since Clark and Lyons used glucose oxidase (GOD) meter for the electrochemical detection of glucose in 1962 [8]. It was used as a stratagem that can convert a specific biological signal into a comprehensible one. Biosensors have many ways to convert signals, mainly in optical [9,10] and electrochemical [11–13] approaches. Optical biosensors convert biological signals into optical signals that can be read by technologies, devices, and people, thus enabling the analysis of biochemical information in biochemical reactions, biological toxins, food safety, and pharmaceuticals. Bioelectrochemical sensors can convert biological signals into readable electrical signals involving voltages, currents, frequencies, and amplitudes. To date, researchers have developed a wide range of biosensors based on metals [14], metal oxides [15], organics [16], and other materials [17,18] that can detect a wide range of human and environmental conditions [14–18]. The most advanced physiological biosensors are often constructed on a hard substrate with common electronic recording hardware. Hence, the monitoring sensors are usually coupled to the skin via straps/tapes with wired interfaces. Table 1 provides a comparison of different materials/techniques for the detection of breast cancer target MicroRNA(miRNA) [19–26]. From the perspective of practicality and comfort level toward final commercialization, there are still a lot of issues that need to be addressed. The problem with existing biosensors concentrates on getting them out of the lab and into the lives of users. Thus, there is a need for highly integrated wearable biosensors. Current wearable devices, typically in the form of miniaturized blocks of wireless flexible electronic/sensing components, are mainly constructed by using soft silicon [27,28] and organic polymers [29–32]. However, both materials have their drawbacks: silicon-based wearable systems struggle to maintain device performance under high strain conditions, while organic-polymers-based wearable devices have limited device performance due to their low carrier mobility.

To address these issues, research efforts have been devoted to replacing the conventional silicon and conductive polymers with emerging two-dimensional (2D) materials. This chapter will review about the 2D materials that have been used for the development of biosensors.

**Two-Dimensional Materials**

Generally, we evaluate the suitability of a material for wearable biodevices by its transmissivity, strain capacity, mechanical capacity, electrical conductivity, biocompatibility, and material size. Compared to conventional 0/1/3-dimensional materials (e.g., silicon and conductive polymers), 2D materials have better conductivity, better optical transparency, excellent mechanical flexibility, and good functionality [[**33**](https://www.mdpi.com/2079-6374/12/11/936#B52-biosensors-12-00936)]. Thus, they prevail in wearable devices as electrodes, resistors, capacitors, and field effect transistors (FETs). The properties and preparations of representative 2D materials, including graphene, TMDCs, h-BN, and MXenes, are discussed below.

*2.1. Graphene and Reduced Graphite Oxide*

As graphene was obtained by Geim et al. in 2004 [[**34**](https://www.mdpi.com/2079-6374/12/11/936#B53-biosensors-12-00936)], it has been overwhelmingly used for the fabrication of wearable systems. Its advantages include ultra-low thickness (~0.6 nm), a large theoretical specific surface area (2630 m2g−1), excellent electronic properties endowed by its carbon atom’s structure (zero band gap and high intrinsic mobility ~ 200,000 cm2v−1s−1), high strength (the theoretical Young’s modulus reaches 1.0 TPa) [3[**5**](https://www.mdpi.com/2079-6374/12/11/936#B54-biosensors-12-00936)], high transparency, and high thermal conductivity (exceeds 5000 W/mK for monolayer graphene) [[**36**](https://www.mdpi.com/2079-6374/12/11/936#B55-biosensors-12-00936)].

Over the past decade, diverse methods have been reported for synthesizing graphene. The search for a method that can reproducibly generate high-quality monolayer graphene sheets with large surface areas and large production volumes is greatly required. Now, several physical and chemical methods have been developed to produce graphene, including the mechanical or chemical exfoliation of graphite [[**37**](https://www.mdpi.com/2079-6374/12/11/936#B53-biosensors-12-00936)], chemical vapor deposition (CVD) [[**38**](https://www.mdpi.com/2079-6374/12/11/936#B56-biosensors-12-00936)], epitaxial growth [[**39**](https://www.mdpi.com/2079-6374/12/11/936#B57-biosensors-12-00936)], reduction of Graphene Oxide [[**40**](https://www.mdpi.com/2079-6374/12/11/936#B58-biosensors-12-00936)], and many other organic synthetic methods [[**41**](https://www.mdpi.com/2079-6374/12/11/936#B59-biosensors-12-00936)]. In addition, graphene can be modified to derive many composite materials, thus providing a more viable option for flexible biosensor fields.

*2.2. Transition Metal Dichalcogenides (TMDCs)*

TMDCs are a class of 2D semiconductor materials with important applications. They are a kind of layered compound denoted by the chemical formula of MX2 (M = transition metals such as Ti, V, Ta, Mo, W, and Re; X = sulfur group elements such as S, Se, and Te). Like graphite, TMDCs have a layered structure in which the monomolecular layers of TMDCs are stacked together by van der Waals forces. Each TMDC monolayer consists of three atomic layers, with a transition metal layer sandwiched between two sulfur layers [[**42**](https://www.mdpi.com/2079-6374/12/11/936#B60-biosensors-12-00936)]. Unlike the zero-energy gap graphene, TMDCs usually possess the semiconductor characteristic with a suitable direct band gap, which is ideal for the construction of photoelectronic devices and electronics devices with high on–off ratios. TMDCs also exhibit an ultra-sensitive response to external stimuli such as mechanical forces, light, electrical potential, molecular, and biochemical perturbations, thus demonstrating great potential for sensor applications [[**43**](https://www.mdpi.com/2079-6374/12/11/936#B61-biosensors-12-00936)].

Like the preparation of graphene, mechanical and chemical exfoliations [[**44**](https://www.mdpi.com/2079-6374/12/11/936#B61-biosensors-12-00936)] are suitable to produce TMDCs. Bottom-up growth method is the newest approach involves various methods, such as CVD [[**45**](https://www.mdpi.com/2079-6374/12/11/936#B64-biosensors-12-00936)], metal–organic chemical vapor deposition (MOCVD) [[**46**](https://www.mdpi.com/2079-6374/12/11/936#B61-biosensors-12-00936)] physical vapor transport [[**4**](https://www.mdpi.com/2079-6374/12/11/936#B64-biosensors-12-00936)**7**] recrystallization [[**48**](https://www.mdpi.com/2079-6374/12/11/936#B67-biosensors-12-00936)], atomic layer deposition (ALD) [[**49**](https://www.mdpi.com/2079-6374/12/11/936#B68-biosensors-12-00936)], and magnetron sputtering, [**50**]

*2.3. Other 2D Materials*

The properties of 2D materials are closely related to their band structures. Other 2D materials such as h-BN and 2D metal MXenes, which have different energy gaps, also attract much attention.

h-BN with a band gap of 6 eV is a rare insulator in the 2D family. The layered structure of h-BN is like graphene, with B and N atoms bonded to each other in the same layer. In general, h-BN is obtained by mechanical stripping, CVD, liquid phase stripping, physical deposition, etc. [[**51**](https://www.mdpi.com/2079-6374/12/11/936#B78-biosensors-12-00936)]. To ensure its gas sensing capability, h-BN is usually functionalized by different modifications [[**52**](https://www.mdpi.com/2079-6374/12/11/936#B79-biosensors-12-00936)].

Metal carbides and nitrides (MXenes) are large in number and varied in category. With their excellent electrical conductivity, large surface area, and flexibility, they are widely employed in biosensing, electrocatalysis, and energy storage, occupying an important position in flexible sensing of 2D materials [[**53-54**](https://www.mdpi.com/2079-6374/12/11/936#B80-biosensors-12-00936)]. In addition, the large layer spacing of MXenes results in large resistance changes during deformation; therefore, they are often used in piezoresistive sensors such as electronic skins [[**55-56**](https://www.mdpi.com/2079-6374/12/11/936#B82-biosensors-12-00936)].

With the increasing development of various 2D materials, scientists’ research goals are no longer limited to 2D planes, but turn to heterostructures, such as graphene/MoS2, MoS2/WSe2, and Graphene/BN [[**57**](https://www.mdpi.com/2079-6374/12/11/936#B84-biosensors-12-00936)]. This kind of heterostructure stacks 2D atomic crystal materials with different electrical and optical properties together to form double-layer or even multilayer artificial materials maintained by van der Waals forces. It is an exotic degree of freedom to enable various fascinating new phenomena in 2D van der Waals heterostructures with adjustable energy band arrangement structures [[**58**](https://www.mdpi.com/2079-6374/12/11/936#B84-biosensors-12-00936)]. The nearly infinite possibilities make the 2D van der Waals heterostructure even more important than the 2D materials themselves in device applications.

**3. Wearable Biosensors Based on 2D Materials**

The ultra-low thickness and excellent physical properties have made 2D materials more attractive in the research of flexible wearable devices. This section describes the fundamental concepts, working mechanisms, and performance of various 2D biosensors.

*3.1. E-Skins*

Electrical skin (e-skin), aiming to visualize the information received by human skin into signals, is one of the significant members of wearable sensors. Numerous types of e-skins were investigated and introduced into services, such as health detection, external environment monitoring, human–computer interaction, and robot control. One important function of human skin is haptics, or its ability to sense pressure, which can sense down to 2 kPa. Hence, the fundamental function of an e-skin is to mimic this pressure sensitivity. To achieve this, various methods are exploited to fabricate e-skin with different modes, including resistive [[**59**](https://www.mdpi.com/2079-6374/12/11/936#B85-biosensors-12-00936)], capacitive [[**60**](https://www.mdpi.com/2079-6374/12/11/936#B86-biosensors-12-00936)], optical [[**61**](https://www.mdpi.com/2079-6374/12/11/936#B87-biosensors-12-00936)], and piezoelectric methods [[**62-63**](https://www.mdpi.com/2079-6374/12/11/936#B88-biosensors-12-00936)].

The first type of e-skin is a resistive electronic skin sensor, which can detect pressure by the change in resistance (R) when deformation occurs on its component materials. It can measure resistance through a constant power supply and output electrical signals in real time with high sensitivity, low cost, and high thermal stability. However, it suffers from drift and hysteresis. As one of the most conductive materials (only 10−6 Ω•m), graphene is a suitable material for resistors [[**64-68**](https://www.mdpi.com/2079-6374/12/11/936#B92-biosensors-12-00936)]. Kireev et al. developed a wearable continuous blood pressure (BP) monitoring platform by using graphene electronic tattoos as human bioelectronic interfaces. These graphene electronic tattoos can monitor arterial BP for >300 min, a period ten-fold longer than reported in previous studies [[**69**](https://www.mdpi.com/2079-6374/12/11/936#B97-biosensors-12-00936)].  This kind of e-skin has shown greatly reduced impedance in detecting electrophysiological signals and, thus, has been used to monitor electrocardiogram (ECG), electroencephalogram (EEG) and electro-ocular signals [[**70**](https://www.mdpi.com/2079-6374/12/11/936#B98-biosensors-12-00936)]. Yao et al. constructed a deformed tattoo with a cracked graphene structure by laser scribing. The e-skin is endowed with contactless temperature-sensing capability by the excellent light and thermal sensing properties of graphene. Moreover, the other properties, e.g., ultrafast responsiveness (6.7 ms) and resilience (13.4 ms), a broad pressure sensing range (2.5 Pa–1.1 MPa), a high sensitivity (2.14 kPa−1), and robust cyclability (2000), make the e-skin more similar to human skin [[**71**](https://www.mdpi.com/2079-6374/12/11/936#B85-biosensors-12-00936)].

The second type of e-skin is a capacitive sensor, which can measure pressure by changing the distance between the upper and lower plates under pressure, then the capacitance is changed and recorded by an electrical output signal [[**72**](https://www.mdpi.com/2079-6374/12/11/936#B85-biosensors-12-00936)-[**74**](https://www.mdpi.com/2079-6374/12/11/936#B85-biosensors-12-00936)]. The advantages of capacitive sensors are low-power consumption, high static stability, and high sensitivity. However, they are more susceptible to external interference and often costly. The sensitivity of the sensor was enhanced by the 3D-microstructured electrodes and the irregular rough micropatterned sensing layer. Therefore, the pressure sensor exhibited striking characteristics, including high pressure sensitivity (6.13 kPa−1), wide detection range (from 20 Pa to 90 kPa), and low operating voltage (0.1 V). As a result, the sensor almost covers the entire sensing range of human skin with the capability of detecting a variety of pressure stimuli, such as radial pulse, human movement, and the touch of very small objects [[**73**](https://www.mdpi.com/2079-6374/12/11/936#B86-biosensors-12-00936)].

The third type of e-skin is the optical sensor, which converts pressure signals into electrical signals through an optical technique [[**74-75**](https://www.mdpi.com/2079-6374/12/11/936#B87-biosensors-12-00936)]. Among all the types of sensors, it is superior in its sensitivity, static terms, linearity, and resistance to drift; however, its instability in the worn situation, high-cost manufacturing, and energy intensity limit their applicability in small, simple, and low-power e-skin devices.

The fourth type of e-skin is a piezoelectric sensor, which converts the mechanical energy of pressure into electrical energy and outputs an electrical signal [[**76**](https://www.mdpi.com/2079-6374/12/11/936#B91-biosensors-12-00936)]. It is advantageous in fast response, energy efficiency, and accuracy, but is disadvantageous in its complexity, high-cost manufacturing, and susceptibility to crosstalk, which makes it difficult for commercialization. However, great efforts have been made to improve its reliability through artificial intelligence (AI).

Another important function of human skin is excretion. Containing various physiological indicators such as electrolytes, amino acids, cortisol, glucose, lactic acid, and excretion serves as a reflection of human diseases. Bariya et al. created a glove to physically collect human sweat to detect physiological indicators [[**77**](https://www.mdpi.com/2079-6374/12/11/936#B107-biosensors-12-00936)]. Cui et al. fabricated a β-cyclodextrin (β-CD)-functionalized graphene-based e-skin to detect K+ and pH in sweat by using a β-CD-functionalized printed flexible graphene electrode as the pH sensing electrode and a flexible silver electrode as the reference electrode [[**78**](https://www.mdpi.com/2079-6374/12/11/936#B108-biosensors-12-00936)]. Liao et al. fabricated a multiplexed sweat analysis e-skin based on a laser-induced 3D porous graphene (LIG) electrode on polyimide (PI) film. For the Na+- and K+-selective sensors, the sensing electrodes were modified by poly (3,4-ethylene dioxythiophene): polystyrene sulfonate (PEDOT: PSS), which is an excellent ion-to-electron transducer. For the pH sensor, an H ion-selective electrode was modified by polyaniline (PANI) using cyclic voltammetry. The LIG-based sensors showed good performance, with sensitivities of 51.5 mV/decade (pH), 45.4 mV/decade (Na+), and 43.3 mV/decade (K+), and the sensing performance was well-maintained under bent states. Good reproducibility, stability, and selectivity were also observed [[**79**](https://www.mdpi.com/2079-6374/12/11/936#B109-biosensors-12-00936)].

Having achieved the detection of physiological indicators on the body surface, researchers have paid more attention to the environmental information in contact with the body surface. A new strategy has been used to achieve the detection of NO2 in the environment by exposing the edge sites of MoS2 and WS2 to construct heterogeneous junctions [[**80**](https://www.mdpi.com/2079-6374/12/11/936#B110-biosensors-12-00936)]. Lee et al. constructed a laboratory jacket by assembling graphene and MXene layer by layer to achieve the detection of NH3. The graphene-hybrid-based fibers have shown good mechanical flexibility (bending for 2000 cycles, resistance fluctuation ±0.2%) and a high sensitivity of 6.77% (∆R/R0 = 6.77%) to 50 ppm NH3 at room temperature [[**81**](https://www.mdpi.com/2079-6374/12/11/936#B111-biosensors-12-00936)].

Significant progress in the development of e-skin has been achieved in recent years; however, as single-function e-skin products have reached a summit, there is a significant opportunity to develop multifunctional e-skins, on which different sensors, communication modules, and power supply systems are integrated.

*3.2. Other Types of Wearable Sensors*

Although much of the current research on wearable sensors is focused on e-skins and contact lens sensors, other types of wearable sensors for different body organs still provide high research value.

As one of the most complex environments in the human body, the mouth contains many electrolytes, microorganisms, enzymes, proteins, gases, DNA, RNA, etc., which have high monitoring value and clinical diagnostic significance. The gases exhaled from the mouth also reflect health indicators. Gases from the human body contain components such as CO, bacteria, and volatile organic compounds (VOCs), which have clinical diagnostic significance for diabetes, cancer, gastritis, etc. Hou et al. proposed a novel humidity sensor functioning by a borophene–MoS2 heterostructure through controlled ultrasonication. The sensitivity was significantly enhanced to as high as 15,500% at a relative humidity of 97%, which is more than 90 or 70 times higher than that of a single borophene or MoS2 [[**120**](https://www.mdpi.com/2079-6374/12/11/936#B120-biosensors-12-00936)]. Liu et al. produced an electronic nose by constructing functionalized reduced graphene oxide to detect four cancer-related marker compounds (ethanol, 2-ethylhexanol, nonanal, and ethylbenzene) at 25 ppm with a linear response. Saliva correlates with blood and can be used to detect inflammation in various diseases [[**82**](https://www.mdpi.com/2079-6374/12/11/936#B121-biosensors-12-00936)].

Mannoor et al. introduced a novel approach to produce wireless graphene nanosensors onto biomaterials via silk bioresorption. Graphene nanosensors are first printed onto water-soluble silk thin-film substrates, then contacted by interdigitated electrodes. Finally, the graphene/electrode/silk hybrid structure is transferred to biomaterials such as tooth enamel or tissue. The resulting device architecture is capable of extremely sensitive chemical and biological sensing, with detection limits down to a single bacterium, while also wirelessly achieving remote powering and readout. The research is considered an important milestone for oral health sensors [[**8**](https://www.mdpi.com/2079-6374/12/11/936#B48-biosensors-12-00936)**3**].

Human hands are used most frequently to deliver signals and information. The role of gloves in wearable devices serves to detect pressure and environmental information and transmit sign language. Li et al. integrated a batch of surface-enhanced Raman scattering (SERS) arrays composed of Ag/MoS2 particles on flame-retardant gloves through screen printing technology, which can detect multiple polycyclic aromatic hydrocarbons (PAHs) simultaneously [[**84**](https://www.mdpi.com/2079-6374/12/11/936#B122-biosensors-12-00936)].

According to statistics, more than 1.57 billion people worldwide suffered from deafness by 2019 and the number might reach up to 2.45 billion by 2050 [[**85**](https://www.mdpi.com/2079-6374/12/11/936#B123-biosensors-12-00936)]. The intervention of cochlear implants and speech recognition sensors would be an effective alleviation. Li et al. reported an artificial eardrum using an acoustic sensor based on 2D MXene (Ti3C2Tx), which can enable a two-stage amplification of pressure and acoustic sensing, thus mimicking the function of a human eardrum for realizing voice detection and recognition. Later, Wang et al. designed a graphene throat patch that is capable of recording deformation resistance through weak vibrations even when no sound is emitted subsequently through AI analysis of the signal [**86**].

**4. Integrated Wearable Biosensor Systems**

The 2D-based biosensors described above are focused on device function rather than system performance. The most advanced noninvasive physiological monitoring systems desire multifunctional and highly integrated sensors, which require more interdisciplinary collaboration rather than the creation of a single-functional sensor. An ideal sensor system consists of a power supply module, a communication module, a computational storage module, a sensing module, and even a drug delivery system (therapeutic module). In this section, we present some of the scientific results that have guided the 2D-based wearable biosensor systems, as well as the components needed to build a complete wearable system.

*4.1. Two-Dimensional-Based Wearable Biosensor Systems*

A high degree of integration is the way forward for the commercial operation of wearable flexible sensors. A popular wearable system must be self-contained. However, due to the multidisciplinary intersection and integration techniques in 2D materials, only a few works can achieve a fully integrated wearable biosensor system.

One representative example is a fully integrated wristband sweat sensor designed by Gao et al. They used commercially available silicon-based integrated circuit technology (more than ten chips) and five functional sensors integrated on a flexible substrate. This wearable device can communicate in real time to a mobile phone terminal or the cloud and compensate for the signal, as well as provide measurement and storage for transmission, with great potential for physiological clinical research and commercialization [[**87**](https://www.mdpi.com/2079-6374/12/11/936#B127-biosensors-12-00936)].

*4.2. Power Supply for Biosensor System*

A significant part of the current research on wearable systems requires external power supply systems to carry out, which include computers, electrochemical workstations, and multimeters. Nowadays, most of the commercial wearable devices use traditional batteries such as lithium batteries and button cells, which limit the miniaturization and application of devices. Hence, efforts have been made on the power supply. Thus far, wearable systems can be expected to be powered by supercapacitors, solar cells, bioelectricity technology, physical hair technology, NFC technology, etc.

Flexible self-healing supercapacitors, a competitive power supply system with high energy density, high charging and discharging efficiency, and excellent mechanical flexibility, meet substantially all the requirements for powering wearable sensing devices. Vu et al. demonstrated a self-healing flexible supercapacitor based on a conductive composite electrode composed of polyurethane and carbon black (PU/CB) using a sandwich structure that provided excellent electrical performance and mechanical flexibility. The device has an electrical energy density of 5.8 μWh/cm2 at 1 mA/cm2 and 91% capacity retention during 10,000 charge/discharge cycles after breaking/healing [[**88**](https://www.mdpi.com/2079-6374/12/11/936#B131-biosensors-12-00936)]. Two-dimensional materials also emerge in this area. Kumar et al. used graphene as a printing ink combined with 3D technology to produce a flexible supercapacitor without any additives [[**89**](https://www.mdpi.com/2079-6374/12/11/936#B132-biosensors-12-00936)].

Physical power generation techniques generally exploit the piezoelectric and Seebeck effects to power a thermodynamic generator by using ambient-skin-temperature differences. Lu et al. designed a flexible piezoelectric nanogenerator through 3D nano-BCZT@Ag heterostructures. The device can be powered by human walking and can deliver 5.85 μA of current (38.6 V) [[**90**](https://www.mdpi.com/2079-6374/12/11/936#B133-biosensors-12-00936)]. Triboelectric nanogenerators (TENGs) are used to power devices by converting friction into electrical energy. Kim et al. showed us a wearable ECG system based on a wearable thermoelectric generator (w-TEG) that can provide more than 13 μW/cm2 of power for more than 22 h through temperature differences [[**91**](https://www.mdpi.com/2079-6374/12/11/936#B134-biosensors-12-00936)]. Guo et al. presented a prototype of an all-in-one shape-adaptive self-charging power unit that can be used for scavenging random body motion energy under complex mechanical deformations. A kirigami paper-based supercapacitor (KP-SC) was designed to work as the flexible energy storage device (stretchability up to 215%). A stretchable and shape-adaptive silicone rubber triboelectric nanogenerator (SR-TENG) was utilized as a flexible energy harvesting device. By combining them with a rectifier, a stretchable, twistable, and bendable self-charging power package was achieved for sustainably driving wearable electronics. This work provides a potential platform for flexible self-powered systems [**92**].

**5. Challenges and Perspectives**

Recent advances in prototypical wearable biosensors with wide-ranging applications across e-skin, contact lenses, and other types of human organ sensors have accelerated the development of 2D wearable biosensor systems. These devices have a wide range of potential uses in the clinical, consumer, and research sectors. They can offer crucial functionality in the fields of clinical medicine, cosmetics, and digital health that conventional electronic systems cannot. However, there is a long way toward final commercialization, especially in materials quality control and system design. Some concerns and potential technical solutions are provided as follows:

Materials quality-control: First, the efficiency of industrial fabrication of 2D materials is a concern. Commercially, traditional silicon-based electronics and organic semiconductors perform better in terms of production costs and efficiency. Developing innovative methods for the large-scale preparation of high-quality 2D materials with low-cost is extremely urgent. Secondly, due to the good thermal/chemical stability and comprehensive study on the graphene and TMDCs, most of the present studies on 2D flexible sensors has concentrated on graphene and TMDCs. Other 2D materials with different energy gaps, such as black phosphorus (BP) and PtSe2, have shown promise for sensing applications. In addition to 2D materials, 2D van der Waals heterostructures have advantages on improving material stability and device performance [[**93**](https://www.mdpi.com/2079-6374/12/11/936#B138-biosensors-12-00936)]. Constructing new biosensing devices using such heterostructures has the potential to enhance sensitivity, selectivity, and stability. In addition, the biocompatibility of the synthesized 2D materials and 2D heterostructures should be investigated to enable their practical applications in bioanalysis.

System design: It appears that the system design has faced greater difficulties than the materials side. First and foremost, the system design must incorporate additional utility. Nobody wants to carry about a full-body wearable device. Instead, consumers wish to detect more information with a single device, which necessitates greater work in terms of powered devices and integrated circuit architecture. Furthermore, the dependability and safety of the system are the key concerns. It is crucial to make sure that the materials employed are biocompatible. More importantly, the biosensor system should be sturdy enough to function without heat, leaks, explosions, or other adverse effects. Reliability is a wide concept that encompasses characteristics such as longevity, accuracy, and interference resistance. In the case of glucose sensors, for example, the common method is to modify the electrode with glucose oxidase, which must be preserved in a specific environment and cannot be operated for extended periods. This is not reliable in practical application. To solve these difficulties, researchers must build more studies in device structure design.

Finally, there is the issue of communication and terminals. Since the day the internet age begun, secure and protocol-compatible communication has always been a requirement. The sensing device and the endpoint should preferably communicate wirelessly. Simultaneously, the terminal should preferably be a smartphone or a cloud-based one, all of which contribute to the proliferation of wearable biosensing devices.

Considering all the mentioned challenges, research on a 2D-materials-based wearable biosensor system has only just begun. All of this necessitates a greater understanding and exploration of 2D materials and biosensing, as well as multidisciplinary research collaboration. In this way, the development of 2D wearable sensing technologies may lead to significant advances in life science, thus promoting human health.

**Author Contributions**

All authors have read and agreed to the published version of the manuscript.

**Funding**

No fund granted.

**Institutional Review Board Statement**

Not applicable.

**Informed Consent Statement**

Not applicable.

**Conflicts of Interest**

The authors declare no conflict of interest.

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