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The era of nano-bionic: 2D materials for wearable and implantable body sensors

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ABSTRACT

Nano-bionics have the potential of revolutionizing modern medicine. Among nano-bionic devices, body sensors allow to monitor in real-time the health of patients, to achieve personalized medicine, and even to restore or enhance human functions. The advent of two-dimensional (2D) materials is facilitating the manufacturing of miniaturized and ultrathin bioelectronics, that can be easily integrated in the human body. Their unique electronic properties allow to efficiently transduce physical and chemical stimuli into electric current. Their flexibility and nanometric thickness facilitate the adaption and adhesion to human body. The low opacity permits to obtain transparent devices. The good cellular adhesion and reduced cytotoxicity are advantageous for the integration of the devices *in vivo*. Herein we review the latest and more significant examples of 2D material-based sensors for health monitoring, describing their architectures, sensing mechanisms, advantages and, as well, the challenges and drawbacks that hampers their translation into commercial clinical devices.

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1. Introduction

Continuous and in real-time monitoring of physiological parameters and biomarkers is a powerful tool for the diagnosis, management, and treatment of chronic and degenerative diseases. For instance, patients affected by chronic diabetes are required to constantly monitor their glucose blood levels, to avoid serious clinical manifestations and further complications [1]. Similarly, it is vital to provide continuous cardiac monitoring in the supervision of patients affected by acute myocardial infarction [2]. Furthermore, *in vivo* neuronal recording is helping in disclosing the mechanisms underneath incurable neurodegenerative diseases, such as Parkinson and Alzheimer diseases [3]. Finally, real-time monitoring of tumoral biomarkers in body fluids is a promising strategy toward cancer prevention [4].

The advent of body sensors offers great promise to better monitor and improve the life-quality of critically ill patients. The use of these innovative monitoring technologies might help improving the efficiency of the medical treatment and, sometimes, has the potential to enhance or even restore human functions [5-7]. For this reason, enormous efforts have been made over the last decades to miniaturize chemical sensors to be small enough to be placed in human organs. [8].

Two dimensional (2D) materials are ideal candidates to produce on-body bioelectronics. They are steady in biological conditions and physiological solutions found in the human body [9]. Moreover, these ultrathin conductors and semiconductors can work as electrical signal transducers or interfaces with neurons and other electroactive cells [9]. For these reasons, the next generation of medical bionic technology is expected to be based on 2D materials. Among various 2D materials, two were mostly explored for this application: graphene (G) and molybdenum disulfide (MoS_2).

Graphene and its derivatives, given their large surface area, remarkable optoelectronic and mechanical properties, possess all the features needed to manufacture on-body bioelectronic devices: sensitivity, specificity, fast response, long-term stability, and biocompatibility. Graphene has a characteristic zero-energy band gap with linear energy dispersion, which confers fast electron mobility ($\sim 2 \cdot 10^5$ $cm^2 \cdot V^{-1}s^{-1}$) and critical current density (10^8 $A \cdot cm^{-2}$) to the material [10]. In fact, graphene is widely employed in electrodes and electrochemical sensors, also due to its wide electrochemical window in water, which makes it an appropriate material to work in a biological environment [10]. Graphene can also provide transparency, which is crucial in several *in vivo* sensing and monitoring implants, such as contact lenses [11-13]. Moreover, the high transparency of chemical vapor deposited (CVD) graphene permits simultaneous sensing and tissue observation obtaining multifunctional bioelectronic device [14]. The mechanical properties of the materials are fundamental parameters when designing *in vivo* bioelectronics. The strong π bonding among C atoms arranged in a honeycomb lattice furnishes remarkable mechanical properties (*e.g.*, Young's modulus = 1TPa) to the implants, protecting them from strain, shear and compressive stress and damage [15]. Furthermore, the single atom thickness of this material allows the implementation of the implant into flexible substrates, enhancing the adaptation of the devices to the *in vivo* tissue and reducing the chances of immune response and rejection [16]. Finally, graphene surfaces can be modified through controlled chemical functionalization by means of either covalent or non-covalent methods [17,18]. In this way receptors such as antibodies, enzymes, and aptamers can be linked to the graphene surface, conferring specificity toward several bio-analytes.

Together with graphene, MoS_2 (and generally transition metal dichalcogenides) were praised among the most promising 2D materials for bioelectronics. This material shares several of the advantageous properties of graphene, such as transparency, flexibility, and biocompatibility. However, due to its unique band gap (1.8 eV for monolayer), MoS_2 has distinctive optical [19] and electrical [20] properties. For example, metal dichalcogenides possess efficient photo-absorption and photocurrent generation capabilities, [21] making these materials ideal candidates for the manufacturing of optoelectronic devices. Piezo resistivity is another peculiar property of MoS_2. The resistivity of this material can be modulated by applying a mechanical strain, which induces changes in the band gap [22]. This property is particularly useful for the development of highly sensitive strains and force sensors, in which the use of MoS_2 allows to achieve gauge factors two orders of magnitude higher compared to metal based or graphene-based devices [23].

Although graphene and other 2D materials possess several common properties, these materials are clearly not interchangeable. Each of them offers a unique set of advantages and limitations that, depending on the specific application, will ultimately determine the effective function and the clinical adoptions. To date, graphene-based devices are the closest to commercialization and to clinical approval, especially because of the intense investigation on graphene chemical-physical properties, manufacturing and reactivity, during the last two decades. Therefore, the set of tools for the development of graphene-based devices is more advanced if compared to other 2D materials. Nevertheless, alternative materials, such as TMDs, Mxenes and perovskites, are fast advancing for analogous applications and since the know-how acquired first for graphene has been transferred to these materials, the manufacturing of innovative sensors was rather facilitated [5,24-28].

Herein, we critically review the latest and, in our opinion, most interesting examples of body sensors and recording devices based on 2D materials. In particular, we focus on devices already employed in *in vivo* studies, which show the highest potential to be transferred to the clinical level. In the introductory section we explain the importance of wearable sensors for health care and prevention, and describe the chemical, physical and mechanical properties of 2D materials, responsible for their relevance in this field (Section 1). In the next section, we overview the architecture and sensing mechanisms of G and MoS_2 based devices: field effect transistors (FET), electrochemical sensors and piezo resistors (Section 1.1). We conclude the introduction by reviewing the factors that currently limit the translation of these technologies into clinical devices. (Section 1.2). In Sections 2 to 6 we categorize the most recent sensors presented in the literature based on tissue/organ of application or implantation (Fig. 1), with the aim to provide an easy to consult and straightforward guide for researchers looking for new technologies for the real-time clinical monitoring. The most extended Section 2 is dedicated to wearable skin sensors divided into two main parts: strain sensors (2.1) and biomarker monitoring from sweat (2.2). The following two sections focus on wearable oral and wearable/implantable ocular devices

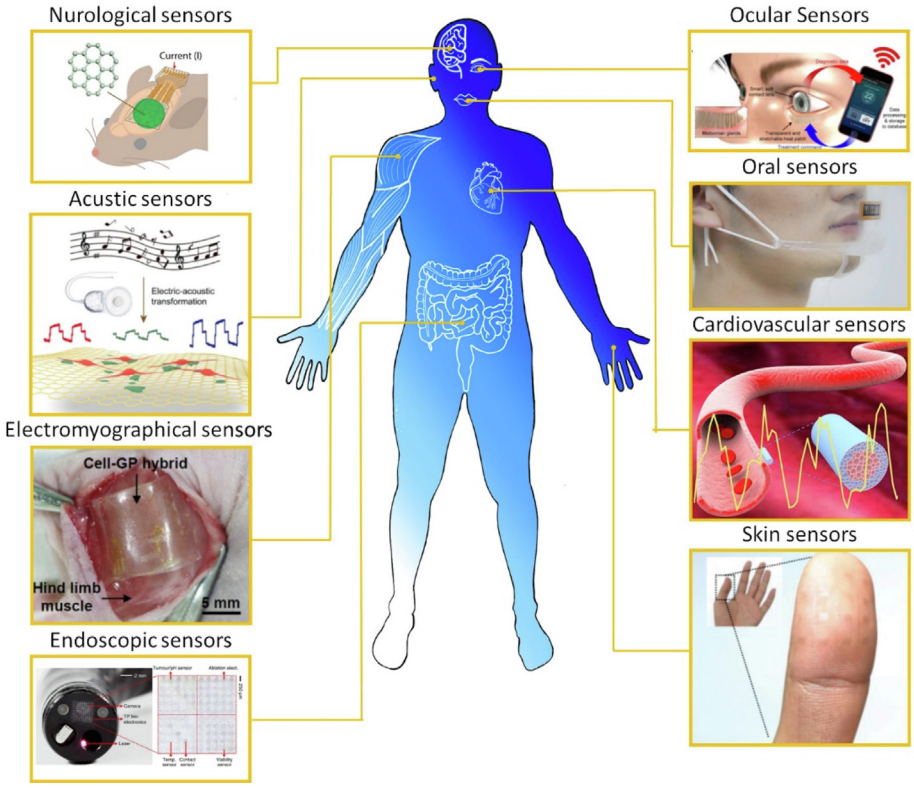

Fig. 1. Summary of the organs monitored with wearable and implantable 2D materials-based sensor up to date, with a representative example for each organ accounted in this review. Figure based on references [6,7,13,14,29-32].

(Section 3 and 4 respectively). Sections 5 and 6 report examples of sensors designed for implantation in the neurological and cardiovascular systems. Section 7 is dedicated to devices located in other organs (*e.g.*, muscular tissues, ears, or intestinal tract). Conclusive Section 8 summarizes the state of the art and the prospects of 2D material-based sensors in healthcare.

1.1. Architectures of the sensing devices

In vivo operating sensing devices must deal with the complexity of biological fluids and matrices, be able to detect low and transient concentrations of analytes and avoid the generation of an immune response from the organism [33-35]. For these reasons, just few architectures are suited for *in vivo* sensing, which can operate in a point-of-care manner and are typically characterized by biocompatibility, fast response, and low limit of detection (LOD) [36]. Three are the 2D material-based devices mainly employed for this scope: field effect transistors (FET), electrochemical sensors and piezo resistors. In Table 1, the devices accounted in this review have been sorted out in terms of monitored organ, electronic architecture, sensing material and recorded signal.

In graphene field-effect transistors (gFET), CVD graphene is deposited as a channel between two metallic electrodes [24]. Such device allows the fine detection of small changes in graphene electrical conductance, due to variations of the electric field in proximity of the material ("field effect") [80]. In a sensor such variations can be exploited to detect electrophysiological inputs or alterations in the biochemical environment surrounding the device [81]. Besides, graphene extraordinary charge mobility confers to gFETs a high transconductance that, together with the low intrinsic noise, allows the detection of electrical signals with elevated signal-to-noise ratio. Apart from graphene, other 2D materials have been integrated in transistors. For instance, the use of MoS_2 allows to obtain both efficient phototransistors, able to transduce photons in an electrical signal with elevated sensitivity and ultrafast response times (below 50 ms) [82,83].

On the other side, electrochemical biosensors are devices that convert the information associated with electrochemical reactions into quantitative electrical signals. Electrochemical sensors can be categorized in three types: potentiometric, conductometric, and amperometric/voltammetric. These devices give in real-time information about the chemical composition of a system, by coupling a specific biological or chemical receptor to an electrochemical transducer. 2D and graphene-based materials have been successfully applied in the development of electrochemical biosensors [10,84,85] as they are efficient transducing platform and offer different chemical and physical routes to immobilize the recognition element [17,18].

Another device architecture, largely employed for strain and force sensors, are piezoresistors, also known as strain gauge devices. These are devices whose resistance changes when a physical stimulus such as force, pressure or mechanical stress is applied. The layered structure of graphene and 2D materials confers them elevated gauge factors, which are reflected in high sensitivity of the devices [86,87].

1.2. Challenges in in vivo sensing

The main challenge hampering the spreading and clinical application of implantable graphene-based biomedical devices is the *in vivo* biocompatibility of these systems. Although the *in vitro* biocompatibility, intended as reduced cellular toxicity, of graphene and related 2D materials has been widely investigated and assessed, [88,89] a different and deeper biocompatibility evaluation is required when translating these materials into clinical use [90]. In fact, *in vivo* biocompatibility might be affected by several

Table 1
Summary of the devices accounted in the review classified on the base of monitored organ, electronic architecture, sensing material and recorded signal.

Location	Sensor type*	Electronic architecture	Sensing material	Recorded signal	Ref
Skin	W/I	Piezo resistor	G/PMA/CA hydrogel	Motion	[37]
	W	Piezo resistor	rGO/PDMS	Motion and ECG	[38]
	W	Piezo resistor	CVD-G/MoS_2	Motion	[7]
	W	Transistor	G/MoS2/cellulose	Motion	[39]
	W	Piezo resistor	G/MoS2	Motion and pressure	[40]
	W	Piezo resistor	Ti_3C_2–MXene	Motion	[41]
	W	Piezo resistor	G/rubber	Breathing	[42]
	W	Piezo resistor	G/Pd/PEDOT:PSS	Breathing and heartbeats	[43]
	W	Piezo resistor	G/PDMS	Breathing	[44]
	W	Piezo resistor	rGO	Breathing	[45]
	W	Piezo resistor	G/nonwoven fabric	Breathing	[80]
	W	Piezo resistor	G/Paper	Breathing	[46]
	W	Electrode	G/PDMS	ECG	[47]
	W	Electrode	G/Kapton®	ECG	[48]
	W	Electrode	G	ECG, temperature, and blood pressure	[49,50]
	W	Electrode	G	EMG	[51]
	W	Piezo resistor	rGO /P(VDF-TrFe)	Voice recognition	[52]
	W	Piezo resistor	G	Voice recognition	[53,54]
	W	Piezo resistor	G/polyimide	Voice and vibrations recognition	[55]
	W	Electrode	G/Au	Glucose in sweat	[56]
	W	Electrode	G/Au or Ni	Glucose in sweat	[57]
	W	Electrode	CVD-G/Pt-NPs	Glucose in sweat	[58]
	W	Electrode	G	UA and Tyr in sweat	[59]
	W	Electrode	MoS_2/AAO	Humidity	[60]
	W	Electrode	rGO/Pt	H_2O_2	[61]
	W	Transistor	G	Cytokins in sweat	[98]
	W	Electrode	G	Cortisol in sweat	[62]
Mouth	W	Electrode	GO	Breathing rate	[63]
	W	Electrode	G	Breathing	[31,64]
	W	Electrode	GO/poly(dopamine)	Humidity	[65]
	W	Electrode	GO or G	Humidity	[66]
	W	Electrode	WS_2/G	Humidity	[67]
	W	Electrode	G, rGO and BC_6N	NOx in breath	[68,69]
	W	Electrode	G, rGO and BC_6N	Acetone in breath	[70]
	W	Electrode	G	Bacteria in saliva	[71]
	W	Piezo resistor	G/Pd	Dysphagia	[72]
Eye	W	Transistor	CVD-G/metal nanowires	Glucose	[11,12]
	W	Transistor	CVD-G/Ag nanowires	MMP-9	[13]
	W	Piezo resistor	G	Intraocular pressure	[73]
	I	Phototransistor	CVD MoS_2/G	Light (Artificial synapses)	[5]
Brain	I	Electrode	PEDOT/GO	Dopamine	[74]
	I	Electrode	G	Brain stimulation	[29]
	I	Electrode	rGO/Au_2O_3	H_2O_2	[75]
	I	Transistor	CVD-G	Brain activity	[76,77]
	I	Electrode	MoS_2	Pressure and temperature	[78]
Heart	I	Electrode	G	ECG	[79]
	I	Piezo resistor	rGO/PPy	Pressure	[32]
Leg (skeletal muscles)	I	Electrode	G/myoblasts	EMG and muscle stimulation	[30]
Ear	I	Electrode	CVD-G	Electric-acoustic stimulation	[6]
Colon	I	Electrode	G/NPs	pH sensing	[14]

*W: wearable I: implantable G: graphene.

complex phenomena such as immune responses, *e.g.,* wound healing response to implantation and formation of glial scars, or chronic inflammation [33,90]. Although establishing protocols for *in vivo* biocompatibility is not trivial, several procedures are starting to emerge to achieve this goal. For example, the expression of the fibroblast growth factor 2 (FGF2) or the glial fibrillary acidic protein (GFAP) in the area surrounding the implant, are useful parameters to monitor the wound healing process and the postsurgical inflammation [5].

Furthermore, detection and study of macro and micro-glial cells by immunolabelling has been employed by Nguyen and co-workers to evaluate the inflammatory response after the implantation of a graphene-based device into the eye of a rat [91]. In fact, the proliferation of reactive micro-glial cells and their amoeboid transformation into macrophages could occur as a response to the implanted material. The number of micro-glial cells in the implanted eyes was not significantly different from the not operated ones, which indicate good biocompatibility of the tested device [91]. Another study demonstrated that the presence of graphene coating around brain intracortical probes strongly reduces the proliferation of astrocytes and microglia around the implant, when compared to the control (the same device, without graphene coating) [92]. At the same time the neuronal network surrounding the device appears healthier with an elevate number of soma and neurites, whilst the control probes (without graphene) after 5 weeks are surrounded by a thick layer of astrocytes and microglia (glial scars) that causes the gradual loss of the signal in time.

Tailoring the mechanical properties of the device to fit the ones of the target organ, has been demonstrated very effective in reducing the post-surgical inflammation process and assure the implant success. Furthermore, the host organism immune response can be significantly reduced by coating the surface of the device with biomimetic coatings, such as proteins and stealth polymers, or by using any biocompatible and flexible materials as support [91,93,94].

Apart from the obvious physiological risks as infection or rejection, an abnormal biological response to the foreign material can originate errant analytical data. [95] In fact, the biological response of the host may produce local changes in the metabolic activity, affecting calibration and sensitivity of an implanted sensor. In this scenario, the implanted device will not trace the real or diagnostically relevant concentrations of the analyte, being unreliable for monitoring the status of patients or taking therapeutic action. Another major challenge for wearable devices, in particular those applied to skin, mouth or eye, concerns their robustness against mechanical stress [96]. In this case, the electrical and, therefore, the sensing performance might be compromised by continuous compression, bending and strains. Finally, the long-term stability and functionality of both wearable and implantable devices is essential for possible commercialization [97].

2. Wearable skin sensors

With an approximate surface of 2 m^2, the skin is the largest organ of the human body. Thanks to its extended surface, easy-accessibility, thin thickness, and mechanical properties, the skin is the ideal organ to non-invasively monitoring of the body motion and vital bio-signals deriving both from dermis and epidermis or from inner organs, blood vessels, and muscles (Fig. 2) [98].

Skin sensors can be classified as non-invasive or invasive: the formers do not infiltrate nor break the skin, while the latter are invasively attached onto or within it through disrupting methodologies. Both kind of sensors can be used to detect a wide range of physiological, biomedical, motion and vital signals correlated to disease diagnosis, health management and human–machine interfaces [99]. However, due to convenient accessibility of skin, the absolute majority of reported sensors are wearable, while invasive ones are just used in few specific cases [61,100].

In the past decades, the development of skin adaptable sensors has been hampered using solid-state technology and rigid metals that can be kept in contact with skin just for short periods, preventing to achieve in real-time and long-term monitoring. Therefore, ultrathin, flexible, and soft systems based on graphene and other 2D materials gained attention, as they can be non-invasively attached to the skin, perfectly adapting to the epidermis curvature. These nanomaterials comprise most of the key parameters required for ideal skin sensors such as transducing capacity, low thickness, softness, stretchability, and adhesion [101]. These features facilitate the incorporation of 2D materials onto different non-invasive supports such as patches, tattoos, and textiles.

When designing skin sensors some fundamental requirements must be considered. For instance, stretchability and softness of the devices are critical parameters since mechanical mismatches with the biological tissue can lead to inaccurate analyses and tissue damage. Stretchability, which is defined as the capability of adapting to intense deformations, is crucial for skin sensors since will be subjected to external harsh strains such as twisting, bending, stretching, etc. In addition, softness is relevant to prevent rupture and to contribute to the device comfort. Softness is related to the Young's modulus of the employed material, that has to match modulus and fracture strain values to the human skin (0.5–1.95 MPa, greater than15%, respectively) [101]. To this end, 2D materials are generally combined with suitable handling polymers to reach the most satisfactory requirements [50,103].

Firm adhesion of the device to skin, both dry and wet conditions, is also desirable to ensure reliable signal recording. Generally, commercial skin sensors possess rigid and thick metal components resulting in an extremely poor attachment. To minimize the weak contact, conductive gels and adhesives are used to improve a signal registered. However, they cannot be used for long periods since they tend to dry or decompose and reduce the

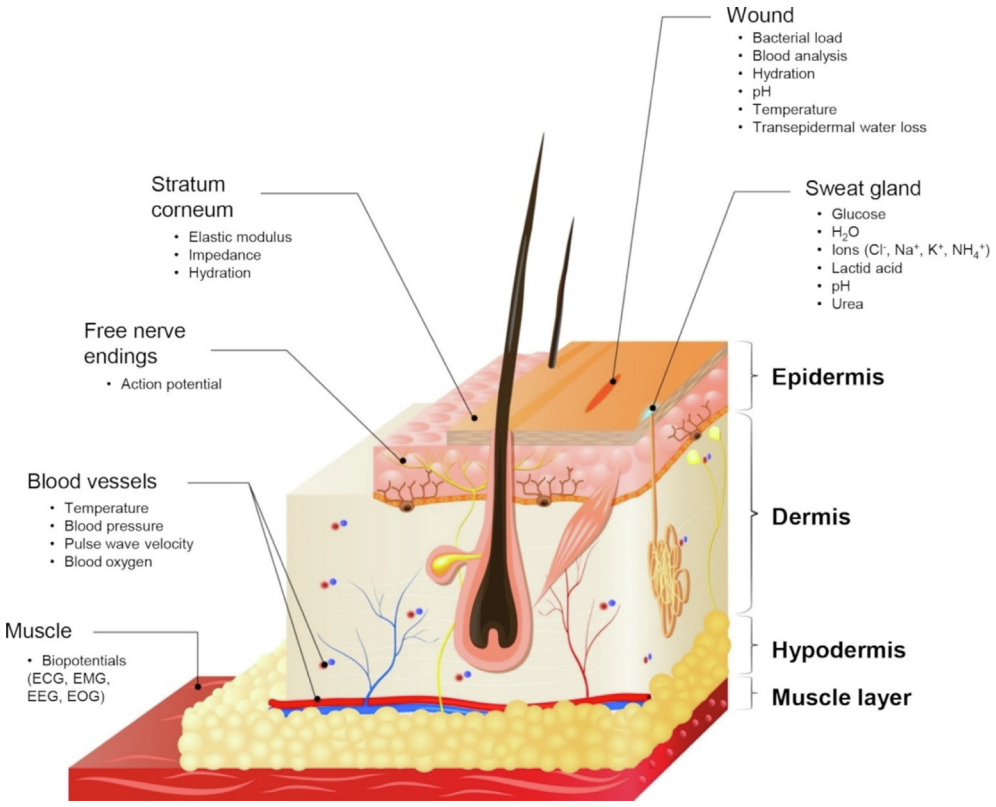

Fig. 2. Physiological and diagnostic signals detectable from skin. Reproduced from ref. [102], Copyright 2017 American Chemical Society.

sensitivity of the devices. To overcome these difficulties, many researchers proposed to use mountable devices or to support graphene on biocompatible and elastic platforms (*e.g.*, polymers and papers) that stay attached to the skin via just van der Waals interactions [49,98,104]. However, the development of skin sensors with simultaneous excellent adhesion and the above-mentioned properties is still challenging.

Biocompatibility is also a key parameter. However, the dermal effects of graphene-based sensors are still understudied, and only few studies have been published about the cutaneous toxicity [105,106]. Two research contributions have highlighted the strong cytotoxicity of graphene to adhere to human skin fibroblast and the probable penetration of few-layer graphene after long exposure time, which might harm the mitochondrial activity associated with plasma membrane [105,107]. In general, the most likely scenario is skin irritation and allergic response, but the cause remains unclear. For example, a recent work has reported that skin irritation caused by graphene, highly depends on the toxicity of the exfoliating agents used [108]. Further detailed analyses on the real toxicity of graphene-based devices after cutaneous exposure is still awaiting [106]. Regarding other 2D materials, the allergic impact on skin and cytotoxicity caused by MoS_2,has been evaluated by Chen *et al.* [109] Cytotoxicity was assessed on different primary and immortalized cell lines both for MoS_2 on surface and in solution. When placed on a solid support, MoS_2 did not significantly alter cell viability, whilst MoS_2 flakes are internalized by cells causing relevant cytotoxicity at concentrations above 0.16 $mg{\cdot}mL^{-1}$. This suggests that the detachment of the material from a solid support might induce adverse effects at relatively high concentrations. Furthermore, the authors tested the allergic impact of metal dichalcogenides on guinea pig skin, an animal model which easily triggers immune response when exposed to allergens. MoS_2 did not induce any allergic effect such as erythema, edema or ulcers.

Another underestimated feature is breathability: through human skin perspiration hundreds of millilitres of water evaporates every day. The remaining water into the device/skin interlayer can generate signal drift and cause skin inflammation. Most skin electronics based on graphene are composed of materials with reduced breathability, which hindered water evaporation. Only wearable sensors with textile structure are presenting good breathing capability [25,110,111]. This design is able to reduce significantly the stiffness, rashes, and skin inflammation while exhibiting excellent monitoring capacities. Two are the major types of physiological signals monitored by skin sensors: physical strain and biomarker concentration. Below, we revised skin sensors based on this classification.

2.1. Strain sensors

Strain sensors are a type of piezoresistive sensors used to monitor motions, pressure, and mechanical stress among other signals. This kind of sensors gained huge importance due to their easy fabrication and operation. However, traditional pressure sensors often fail in achieving wide working ranges and elevated sensitivities simultaneously, as required for this application. Recently, 2D materials became promising candidates to overcome this issue, due to their layered structure able to provide piezoelectric effect with elevated gauge factors (GF). As a result, devices based on these materials presents high sensitivity which permits the detection of the weakest physiological signals [86,87]. Further strategies to improve the sensitivity of the devices consist in introducing porous structures, such as hydrogels, aerogels, and 3D porous networks, or micropatterning techniques [31,32,39,40,64]. Overall, wearable strain sensors have been largely employed to monitor body movements, respiration rate, electrophysiological signals, and speech vibrations.

2.1.1. Body movement monitoring

The so-called motion or movement sensors are devices specifically designed to precisely detect external body movements, mainly from muscles and limbs. Such systems may play a crucial role as a tool for prevention, diagnosis, or rehabilitation of multiple diseases, such as neurodegenerative and neuromuscular diseases or involuntary muscular disorders.

Body movement sensors usually include in their design specific adhesive components that ensures total adhesion to skin and reliable signal recording. Cai *et al.* developed a sensor to monitor human body motions by combining graphene foam with polyacrylamide/calcium-alginate (PAM/CA) hydrogel. The authors used chitosan as adhesive interface to allow the fixation of the hydrogel onto the skin. The resulting device showed an elastic modulus analogous to the one of skin (8–90 kPA), with a wide range of strain (up to 500%), high sensitivity and remarkable durability (up to 1,000 cycles). The device was tested as a wearable sensor on human body. Moreover, the *in vivo* biocompatibility was demonstrated by implanting the device subcutaneously in mice [37]. In a second example, Chun *et al.* reported a simple, low-cost and scalable fabrication method to produce reduced graphene oxide (rGO)-coated fabric strain sensors. In this case, the authors used a polydimethylsiloxane (PDMS) octopus-like pattern (Fig. 3), placed on the side in contact to the skin, to improve the adhesion both in dry and wet environments. This PDMS-coated rGO fabric sensor showed not only efficient detection of body motions but as well of electrocardiogram (ECG) signals and speech vibrations both in dry and wet conditions, with extremely sensitive piezoresistive responses and low detection limits for pressure and strain [38].

Apart from graphene and graphene oxide (GO) other 2D materials can be used to manufacture effective strain sensors. Thanks to its elevated gauge factor and tunable band gap, MoS_2 is an extremely interesting candidate for this application. Park *et al.* presented a fingerprint tactile sensor fabricated with MoS_2 transferred over CVD grown graphene electrodes [7]. Compared with conventional strain gauges, the MoS_2-based strain sensor showed good optical transparency, high mechanical flexibility, and elevated GF. Furthermore, the ultrathin nature of the sensor (below 75 nm) and its extreme flexibility allows the device to perfectly adapt to the tiniest irregularities of skin, such as the fingerprints. This technology in the next future, could have the potential to restore human functions, such as tactile sensibility lost in damaged or burned skin.

Sahatiya *et al.* reported another strain sensor based on MoS_2. In this case an ultra-low cost (G)–MoS_2 FET was fabricated using biodegradable cellulose paper [39]. MoS_2 with nanoflower morphology was hydrothermally grown over paper soaked in exfoliated graphene. The source and drain of the FET were drawn using a pencil. In spite of the low-cost of the materials and the simple design, the as fabricated G/MoS_2 transistor exhibits on/off ratio of ≈99 with carrier mobility of 18.7 $cm^2\ V^{-1}\ s^{-1}$ and were used as sensor able to detect low strain values down to 0.5%. By interfacing the sensor with a microcontroller, the authors were able to build a wearable prototype enabling human finger motion monitoring.

On the same line, three-dimensional porous networks based on graphene and MoS_2 were exploited to manufacture a strain-pressure sensor with elevated sensitivity and durability [40]. The addition of MoS_2 planar sheets to the graphene network, induces the formation of MoS_2 islands with a cracked paddy shape. Such nanopatterned distribution of MoS_2 onto the graphene network surface can improve resistance variation upon external strain and pressure. Compared to previously reported graphene porous network, this hybrid material showed improved sensitivity and excellent durability under repeated pressure cycles. When attached

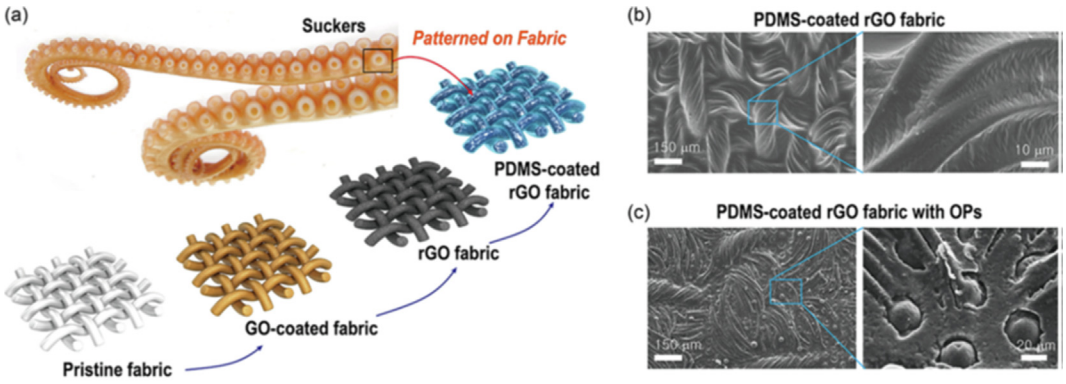

Fig. 3. Nature inspired materials can improve the skin adhesion of the sensors: (a) Schematic illustration of the octopus-like patterned (OPs), rGO-fabric coated with rGO and PDMS. Scanning electron microscope (SEM) images of plain fabric (b) and OP-engraved fabric (c). Reproduced from ref. [38], Copyright 2019 American Chemical Society.

onto the human temple and neck the sensor can detect motion signals such as neck bending and eye blinking.

As well, MXenes have been used to fabricate efficient strain sensors for human motion monitoring. Ma *et al.* manufactured a Ti_3C_2–MXene based flexible piezoelectric sensor with interdigital electrodes [41]. The sensor showed high compressibility, high sensitivity, fast response, and mechanical reversibility. The working mechanism for the piezoresistive sensor, based on change of resistance upon strain-pressure, was demonstrated monitoring the change in the interlayer distance through in situ transmission electron microscopy (TEM).

2.1.2. Respiratory rate monitoring

Strain sensors have also found wide application in respiratory rate monitoring through chest fixation. Boland *et al.* developed a cheap strain sensor based on liquid-exfoliated graphene infused into commercial rubber [42]. The resulting graphene-infiltrated elastic has a gauge factor of 35 and resistance between 4 MΩ and 57kΩ, depending on the volume fraction of graphene. The resistance of the device is determined by the strain applied to the band, registering increases up to 4 orders of magnitude when 800% strain is applied. By placing the band horizontally across the rib cage, real-time breathing could be recorded. Another wearable strain sensor to monitor simultaneously the heartbeat and respiration, was developed based on graphene, palladium film, and highly plasticized poly(3,4-ethylene-dioxythiophene):poly(st yrenesulfonate) (PEDOT:PSS) [43]. PEDOT:PSS was used as a conductive supporting substrate for graphene/palladium at the high strain range. The resulting strain sensor displayed high sensitivity at low strains (0.001% engineering strain) and an extensive working range up to 86%, which are essential to detect heartbeat (small strain, shorter time interval) and respiration (large strain, longer time interval) at the same time (Fig. 4).

In addition, textile sensors have been used to monitor respiration due to their low-cost and green textile material. A simple-structured and low-cost strain sensor was composed of graphene woven fabrics, PDMS, and medical tape, and was applied to detect weak human motion signals, including breathing in both resting and active states [44]. In a second example, synthetic fiber (cellulose acetate fiber, CAF) bundles were used to adsorb rGO sheets, leading to gaps in the microstructures of the sensors with bundle alignment perpendicular to the strain axis, which decreases the conductance of the sensor [45]. Ouyang J. and co-workers have developed a facile and cost-effective dip-and-reduce method of graphene-based wearable sensors integrated into the nonwoven fabrics (NWF) [112]. The as-obtained graphene-NWF sensors displayed negative gauge factor at small strain.

Inspired by the skin epidermis, low-cost, easily prepared, and soft/wearable pressure sensors based on graphene and abrasive paper have also been reported to detect physiological activities, including respiration [46]. In these sensors with random distribution spinosum (RDS) microstructure, abrasive paper was used as the template and graphene as the sensing material. Both experiment and simulation demonstrate that the effective interlocking of RDS layers results in high sensitivity and an extensive linear range.

Further devices for the monitoring of respiration rate, wearable on the mouth, will be reviewed in the section oral wearable device.

2.1.3. Electrophysiological sensors

There are several physiological signals, in some case known as biopotentials, that are generated by the cardiovascular system, which are non-invasively detectable from skin. Alteration of these signals are related to possible anomalies and cardiovascular diseases. For example, pulse waves generated by the arterial system elasticity are employed for early diagnosis of arteriosclerosis; [113] phonocardiogram analysis monitor the sound produced by the heart, whose frequency and intensity are related to the myocardial function; the beat generated by the heart and the whole vascular system produced mechanical vibrations on the chest and on the surface of the body, which are also informative and employed to record a seismo-cardiogram (SCG) or a ballistiocardiogram (BCG) [114]. In the field of wearable biosensors, there is great interest in developing devices able to detect one or more of the above physiological signals for a reliable, highly sensitive real-time cardiovascular monitoring and not requiring hospital environment.

In general, the complex electrical activity of the heart is usually analysed through ECG, which is the most employed tool to monitor heart function. Current ECG machines record the difference of potential generated by the heart using Ag/AgCl wet electrodes, where conductive gel is required between electrodes and the skin. However, such gels are easy to deteriorate, strongly affected by patient movements and in some cases causing skin reactions and allergies. Therefore, alternative dry electrodes for ECG can be highly interesting.

Zang et al. employed laser-induced graphene (LIG) supported by PDMS layers to fabricate a six chest-lead dry electrode [47]. This device easy adhere to the skin, is very robust (keeping low impedance of 199 kW at 20 Hz after repetitive ultrasound washing) with a high signal-to-noise (SN) ratio. Interestingly, this device can be customized according with patient anatomy and allow the application of a six-lead at once (Fig. 5), with performance comparable with the commonly used 12-lead ECG. An alternative inex-

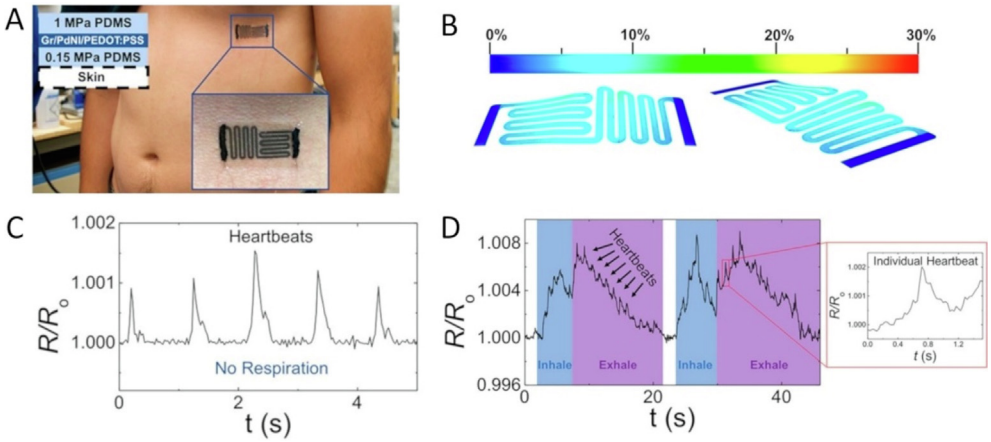

Fig. 4. Strain sensors encountered potential application in respiratory monitoring: chest fixation enables on-body testing of the G/Pd/PEDOT:PSS material, patterned into a serpentine strain gauge design. (a) Photograph and side view schematic of the wearable G/Pd/PEDOT:PSS sensor on the body of a human subject. (b) Finite element analysis (FEA) of the patterned G/Pd/ PEDOT:PSS sensor as the material accommodates stress stemming from a normal force, simulating the force stemming from a heartbeat and/or respiration. Piezoresistive response of the patterned G/Pd/PEDOT:PSS sensor to simulations of (c) obstructive sleep apnea and (d) normal sleep by the human subject. Reproduced from ref. [43], Copyright 2019 American Chemical Society.

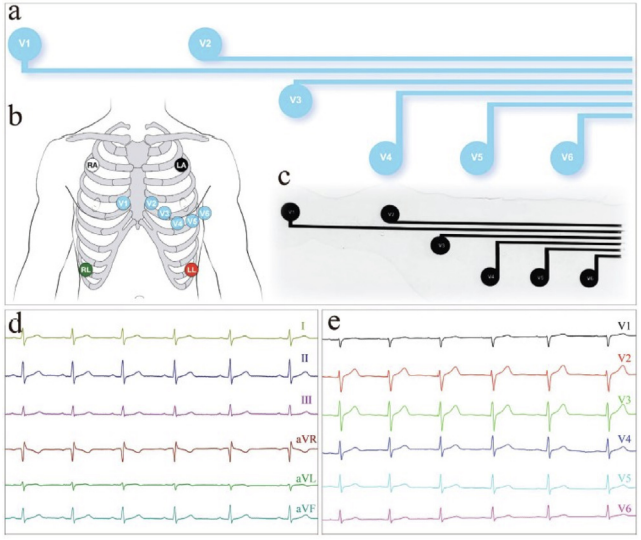

Fig. 5. Laser-induced graphene (LIG) is a cheap and emerging material that allows to design customized electrodes according with patient anatomy. a) Scheme of integrated staff-shaped chest-electrode patterns (V1–V6). b) Positions of LIG/PDMS electrodes on human chest. c) Photograph of LIG/PDMS electrodes. d,e) ECG signals (t = 5 s) recorded by LIG/PDMS electrodes. Reproduced from ref. [47], Copyright 2021 Wiley-VCH GmbH.

pensive formulation has been proposed by Romero and co-workers: they employed a foam of porous graphene, obtained by laser-induction of flexible carbon rich Kapton® substrate, as component to develop their electrode for ubiquitous ECG [48]. A circumference of 10 mm diameter was photothermally patterned onto a Kapton® HN tape using a laser diode, generating, also in this case, a LIG area. The electrode was placed safely on the skin using transparent polyurethane (PU) film and a polyacrylate adhesive. The performance of the electrode was tested, applied on the wrist of volunteers, and the ECG recorded was highly comparable with the ECG obtained with commercial Ag/AgCl wet electrodes, with the typical pattern that includes P wave, QRS complex, and T wave.

Akinwande *et al.* were among the firsts to develop graphene-based electronic tattoo (GET) sensor for ECG measurements, but also employable to measure electromyogram, electroencephalogram, skin temperature and hydration [49]. The tattoo was carved into filamentary serpentine ribbons to improve the stretchability of the device. To measure ECG, the GET sensor (with a measured thickness of 463 ± 30 nm) was transferred on the human chest, in contact with the skin, working as easily as a temporary transfer tattoo. The signals recorded were comparable with those recorded by using commercial gel electrodes. The same authors recently reported an updated overview about GET technology and their versatility toward detection of biopotentials from different sources, including potential applications for heart and blood pressure monitoring [50]. Overall, the advantages of this methods are their simple preparation, their proved biocompatibility, their transparency, and softness, which allow obtaining reproducible signals also during natural skin stretches and movements. Current challenges for these devices concern: i) the improvement of the reproducibility between devices, mainly depending on CVD graphene sources and providers and ii) optimize the durability of the device without compromising softness and skin wearability.

Another type of electrophysiological signal that can be monitored is electromyography (EMG), although there is not much literature in this regard. Kim and co-workers developed a non-invasive nanomembrane system for real-time continuous monitoring of craniofacial muscles, specifically for masseter muscles that are critical for mastication [51]. These kinds of skeletal muscles have low regenerative capacity and one of the main challenges facing *in vivo* models is the lack of effective tools to monitor the regeneration and recovery of injured craniofacial muscles. The authors fabricated a miniaturized portable wireless electronic device based on ultrathin, low-profile, lightweight, soft, and stretchable graphene sensors that could be laminated to the skin over the target muscle to record EMG activity on free moving mice. They evaluated the efficiency of their device by *in vivo* monitoring of active mice during mastication and demonstrated that their sensor also allowed highly sensitive electromyogram detection of the recovery of the muscle after surgical transplantation.

2.1.4. Speech vibration/voice recognition

The studies of wearable sensors used for speech recognition increased significantly in the last years. Usually, the common sensors used for motion monitoring and other pressure movement detections are employed. Speech recognition is tested through the resistance variation coming from talk vibrations of a tester [38,44,115]. Such application has a great potential in human–machine interaction and speech ability recovering. In addition to the

common properties of strain sensors, speech detectors also require ultra-sensitivity to capture the subtle muscle movement during speech and rapid response speed. A static pressure detector was fabricated self-assembled films composed of nanofibers of neutral viscoelastic P(VDF-TrFe) (Poly(vinylidene fluoride-co-trifluoroethylene)) and rGO, which showed high sensitivity (15.6 kPa^{-1}), low detection limit (1.2 Pa), long-term stability (100,000 cycles) and fast response (5 ms). The authors demonstrated the ability of their sensor to detect a feather or a rice grain. Furthermore, the sensor resulted an efficient method for voice recognitions, able to differentiate between several words from a tester spoke and showing different waveform patterns for different pronunciations [52]. In another example, ultrahigh sensitivity of the device was reached with "compression spring" architecture of a graphene-based fiber, with a detection limit of 0.2% strain and a response of less than 100 ms. The device was successfully applied for accurate speech recognition and, furthermore, for real-time monitoring and recording of complex robot movements, as the authors proved with the "Gangnam Style" dance [54].

Wang and co-workers designed a flexible and wearable graphene woven fabrics (GWF) adhered on elastic double-sided tape film with high-precision speech acquisition and recognition through muscle movement, regardless of whether the sound is vocalized or not. The authors were able to decrease the pathways and, thus, increase the resistance of their device by introducing high-density randomly dispersed cracks along the film network upon being stretched. The ultra-high sensitivity of rapid and low-frequency speech was demonstrated with English letters, Chinese characters and tones and whole phrases and sentences, in both from a tester spoke and pre-recorded sounds [53].

One of the most advanced works in speech sensing is a wearable artificial throat able to detect and generate sounds (frequencies between 100 Hz and 40 kHz) simultaneously (Fig. 6). The device is based on a LIG on polyimide substrate and showed high sensitivity, low limit detection, high thermal conductivity, and low heat capacity, thus making it an excellent candidate for thermoacoustic sound source. Furthermore, such intelligent artificial throat exhibited capability to recognize different intensities and volumes of hum, cough, and scream, convert those unclear throat vibrations into controllable sounds and, thus, differentiate between different pronounced words and sentences. Overall, this work paved the way to specific phonation recognition, providing assistance and speech rehabilitation training for disabled patients [55].

2.2. Biomarkers from sweat

Sweat, secreted by the skin, is a biological fluid containing various ions, hormones, small proteins, acids and metabolites which reflect specific information about health. Human sweat is thus the most ideal biofluid for non-invasive real-time health monitoring of biomarkers through chemical sensing [116]. For instance, measuring levels of glucose in sweat, which are directly related to the glucose in blood, is a tool to monitor the chronic condition of diabetes.

The most conventional methods to detect glucose are based on invasive methods through blood extraction. But recent developments of skin chemical sensors of graphene allow detecting low traces of glucose in sweat. [117] Wearable glucose sensors are mainly based on electrochemical oxidation of glucose through enzymatic or non-enzymatic sensing, in which graphene is employed as electrode. Graphene enhances the electron transfer between the electrode and the enzyme or glucose, for enzymatic and non-enzymatic oxidation of glucose, respectively. In addition, graphene can mediate the oxidation of H_2O_2 (intermediate product in the enzymatic process of glucose). For example, Lee and co-workers fabricated a multifunctional device using a gold-graphene hybrid to be applied on skin for real-time monitoring of glucose in sweat and simultaneous controlled administration of antidiabetic drugs through the skin. [56] The device consists of a bilayer structure of gold-doped CVD graphene modified with glucose oxidase, which shows high conductivity and mechanical stability, obtaining accurate electrical signals from the skin. Thus, when the sensor exceeds a glucose threshold, thermal activation of the drug-loaded microneedles is triggered. The sensitivity of the glucose sensor was successfully tested in two healthy volunteers, and diabetic mice models were employed to study the therapeutic effect of the temperature responsive drug delivery system. Such device is a very strong example of combining continuous chronic disease monitoring with automatic "on demand" treatment.

Other 3D structures based on graphene with increased and controlled porosity are suitable for wearable glucose sensing. In fact, such materials present higher surface area and an enhanced loading capability of enzyme. For instance, Zhu *et al.* prepared 3D LIG foams and fibers as base of the electrode of a flexible non-enzymatic sweat glucose sensor. The sensor exhibited high sensitivity in human sweat. In addition, a large linear range (0–30 mM) have been achieved, by using Ni and Au coating, with high glucose selectivity in the presence of typical interfering substances, *e.g.*, ascorbic acid, dopamine hydrochloride, uric acid, acetaminophen, lactose, sucrose, fructose, lactate, urea, glycine, and mM concentrations of NaCl, KCl, $CaCl_2$, and $NaHCO_3$. [57].

The sampling strategy of sweat is fundamental in the design of wearable biosensors, to ensure always fresh analytes, and control the volume of the physiological fluid. For example, glucose can be sampled from the interstitial fluid via electro-osmotic extraction follicular pathways in the skin. With this technique interstitial fluids can be drawn through the skin and captured into a known,

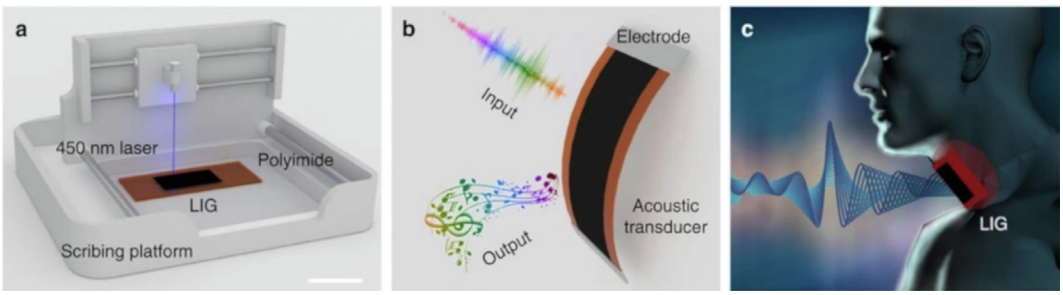

Fig. 6. Strain sensors with ultrahigh sensitivity to detect soft muscle movements are being applied for speech recognition through talk vibrations. As example, a schematic representation of a LIG graphene-based artificial throat is shown: (a) One-step LIG fabrication. PI is converted into LIG by laser irradiation at 450 nm (Scale bar, 2.5 cm). (b) LIG has both the ability of emitting and detecting sounds. (c) The artificial throat is able to detect the movement of throat generating controllable sounds. Reproduced from ref. [55], Copyright 2017 Nature.

small volume, allowing systemic glucose detection without need of previous calibrations of the system. To do so, a miniaturized array of electrodes, suitable for electro-osmotic extraction and electrochemical sensing is required. Lipani *et al.* coated this array of electrodes with a CVD graphene-based film decorated with Pt nanoparticles to enhance the sensitivity. [58] A glucose oxidase-bearing hydrogel works as biofluid reservoir. With this design the sensor can detect glucose with a sensitivity of 37 μA mM^{-1} cm^{-2} and LOD of 0.76 μM.

Another strategy to achieve continued sampling of sweat is the use of microfluidic devices. Yang *et al.* presented a sweat sensor that is entirely laser engraved enabling wireless continuous monitoring of uric acid (UA), Tyrosine (Tyr) and vital signs. It consists of a LIG chemical sensor and a laser-engraved microfluidic device that enables continuous sweat sampling. Due to the fast electron mobility, elevated current density and extended surface area, this graphene-based sensor can rapidly and accurately detect UA and Tyr in human sweat in situ. Furthermore, the manufacture methodology is easily scalable since all the key modules composing the devices are fabricated with a broadly diffused CO_2 laser engraving approach. [59].

Monitoring sweat rate is crucial for the reliable quantification of molecular concentration in sweat. For this reason, innovative solutions are required, to accurately determine the volume of this biological fluid in wearable biosensors. Mondal *et al.* introduced an anodic aluminum oxide (AAO) coated with MoS_2 honeycomb structure as a resistive sensor for humidity. [60] The highly porous MoS_2 honeycomb-like can amplify the sensing performance of the device due to the open pores and wide absorption surface. The proposed sensor exhibited a sensitivity of 2 orders of magnitudes higher compared to the MoS_2 film-based humidity sensor. Furthermore, the sensor showed faster response and recovery times. The authors integrated the devices in a wearable platform and used it to accurately determine the regional sweat rate, showing promising potential for the next generation of wearable sensors. In addition, the versatility of the devices was demonstrated applying it for human breath monitoring, speech recognition and noncontact sensation of human fingertips.

Sometimes the possibility of sensing extremely low molecular concentrations of analytes is essential to provide rapid and early detection of human pathologies. Wearable sensors discussed above may not always reach such resolution of detection and, therefore, minimally-invasive transdermal sensors can be a suitable solution. For instance, the usage of microneedles for detection of low concentrations of transdermal H_2O_2 may play a vital role in the diagnosis of diseases with cell damage that can lead to senescence, neurodegeneration, and even cancer. Jin *et al.* reported a nanohybrid electrochemical biosensor based on microneedles embedded with rGO and Pt nanoparticles and showed efficient transdermal and painless detection of H_2O_2 *in vivo* on mice. [61] In order to avoid mechanical destruction and protect the nanoparticles during skin insertion, the authors recovered the patch with a water-soluble polymer layer, which was later degraded after inserted, thus preserving the sensitivity and sensing capacity of the device.

Apart from glucose, several analytes and biomarkers can be detected in human sweat. Recently, Hao *et al.* developed an aptameric dual channel gFET for the in-situ detection of cytokines such as interferon (IFN), interleukin (IL-6), and tumor necrosis factor (TNF) in COVID-19 patients (Fig. 7). [26] Abnormally elevated levels of cytokines are considered prognosis biomarkers for severe or critical progression of COVID-19 and of great significance to detect and treat COVID-19 patients before they become critically ill. The device was fabricated on flexible substrates and integrated in a wireless device to enable wearable applications and continues monitoring of cytokines in hospitalized patients. Thanks to the dual channel design and TWEEN 80 passivation, false response signals originated from pH, ionic strength variations and nonspecific adsorption of complex components in biofluids can be minimized or eliminated. The gFET sensing capability toward IFN, IL-6, and TNF was tested in different biofluids such as plasma, saliva, sweat and urines. The sensor allows to rapidly detect the analytes (7 min) with the LODs of $476 \cdot 10^{-15}$, $608 \cdot 10^{-15}$, or $611 \cdot 10^{-15}$ M, respectively.

The hormone cortisol in sweat is related to acute and chronic stress that has a negative impact on human health. Chronic stress is considered the health epidemic of the 21st Century. Thus, there is a great demand for detection systems capable of supporting quasi-continuous measurements of cortisol levels to understand and assess endocrine response to stress. Recently, Torrente-Rodriguez *et al.* developed a wireless sensor patch for monitoring cortisol in human sweat using a LIG electrode. [62] As glucose sensing, the detection of this "stress hormone" needs a specific bioreceptor for its recognition such as antibody. Therefore, the LIG electrode was modified with anti-cortisol antibody, on which there was competition between sweat cortisol and horseradish peroxidase labelled with cortisol. In this manner, current generated from enzymatic reduction of H_2O_2 was related to the amount of cortisol. The device showed a limit of detection of 0.08 $ng \cdot mL^{-1}$, and it was successfully evaluated in human by a pilot human study, which revels fluctuations of the ultra-low levels of sweat cortisol for 6 days.

Monitoring ion concentrations in sweat is also crucial to evaluating human health. For example, Na^+ and K^+ cations in sweat are related to dehydration, anaerobic metabolism, hypokalemia, and hyponatremia; while Cl^- detection in sweat is used to diagnose cystic fibrosis. Wearable ion detection on skin is mainly based on electrochemical sensors with all-solid-state ion-selective electrodes (ISEs) modified with the corresponding ionophore. They present easy integration (avoiding the use of reference solution), stability, miniaturization, and fast response. [116] In these devices, graphene has been widely studied as ion-to-electron transducer because increases the hydrophobicity of the electrode surface, provides a high surface area, excellent conductivity, electrocatalytic activity and accelerates the electron transfer during ion exchange between an electrode and the solution. [27,28] Particularly, graphene oxide and exfoliated graphene derivatives have been employed because they can be dispersed in solvents for ink production, which allows creating patterned electrodes. Although the research of graphene-based sensors for skin has made remarkable achievements, there still exist some limitations that nanomaterials are not solving yet. Except few examples, most of graphene derivatives generally cannot detect target analytes by themselves, so they are often modified with biomolecules. This fact limits their applications because it increases production costs, in addition to their poor stability.

3. Wearable oral sensors

Sensors wearable on the mouth region can be categorized in 3 main types: i) strain/pressure and humidity graphene-based sensors to monitor respiration, ii) biosensors for the detection of chemical and biological species in breath and saliva, iii) piezoresistive sensors to monitor swallowing activity.

Respiration is one of the most critical and monitored physiological signals in hospitalized patients, therefore the search of innovative and non-invasive technologies for its in real-time detection and monitoring always attracted interest. A widespread approach to monitor respiratory rate is to install a pressure sensor on a wearable mask to detect the pressure changes caused by the breathing airflow. The achievement of simultaneously large working range and elevated sensitivity is extremely important for this application.

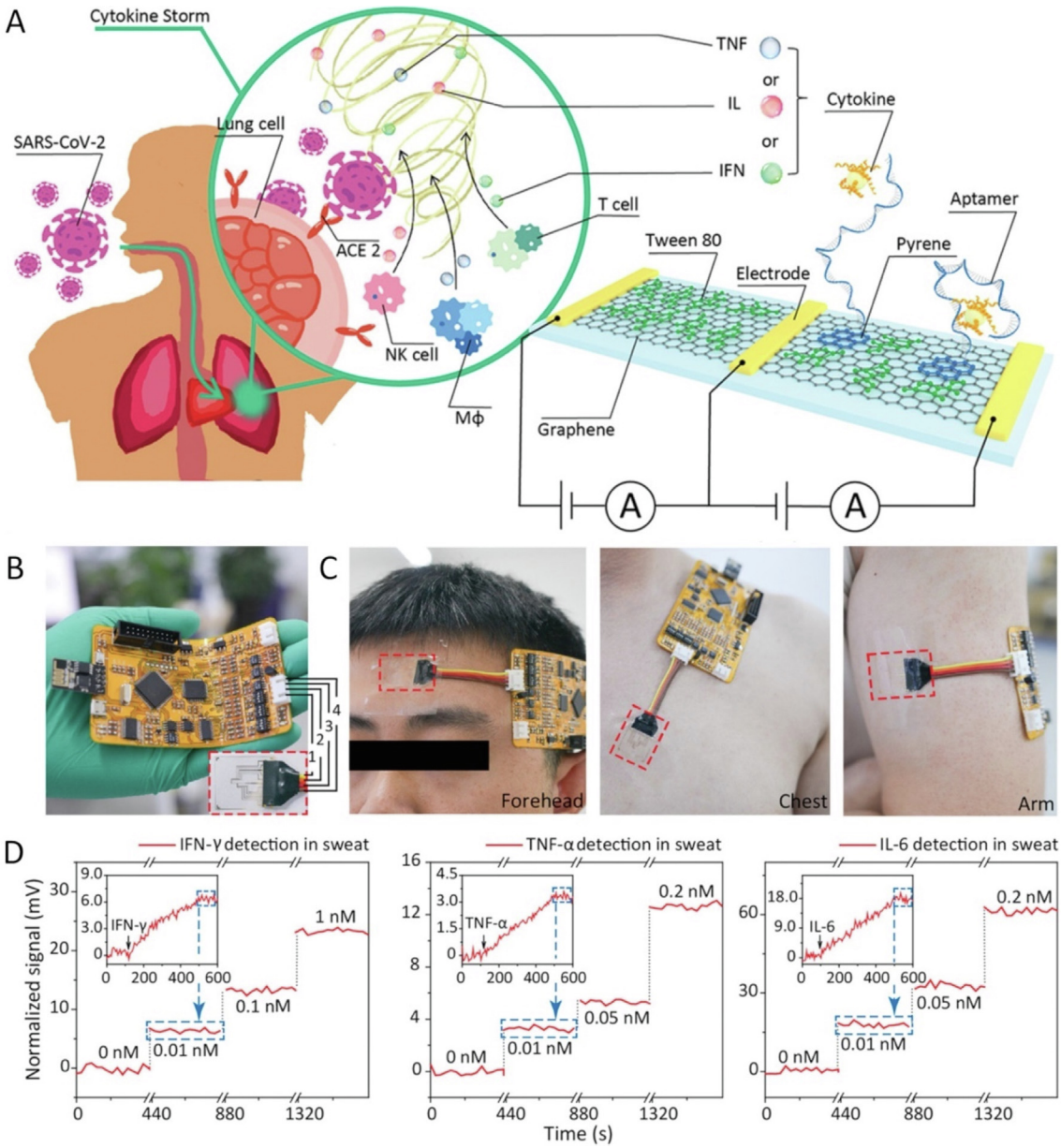

Fig. 7. Human sweat is a biofluid rich in biomarkers for non-invasive real-time health monitoring through chemical sensing. In this example, a gFET biosensor is developed for the detection of cytokine storm syndrome caused by COVID-19: (a) Scheme of the aptameric dual channel of the gFET biosensor (b) Photograph of the flexible and wearable aptameric gFET device. (c) The device worn on different human body parts *e.g.*, forehead, chest, and arm. (h) Time-resolved, and in real-time measurement of IFN, TNF, and IL-6 in human sweat. Reproduced from ref. [26], Copyright 2021 Wiley.

In this, graphene-related materials can help and be used to design high-performance pressure sensors.

For instance, Tao *et al.* reported a sensor obtained by soaking tissue paper into GO, and then reducing it by thermal approach (Fig. 8). [63] The as-prepared device displays high sensitivity (17.2 kPa^{-1}) and a large working range (0–20 kPa). This device was fixed on a transparent mask and used to monitor human respiration at rest and during intense physical activity. The results demonstrated that the respiration rate changed from 16 times·min^{-1} before exercise to 68 times·min^{-1} after exercise, in good accordance with the fatigue level. Thanks to its wide working range and high sensitivity, such pressure sensor, apart from respiratory detections can be applied in pulse detection, voice recognition, and intense motion detections.

Another approach to obtain highly sensitive pressure sensors with wide working range is to create patterns in graphene oxide layers by laser scribing. Qiao *et al.* using this approach developed multilayer graphene epidermal electronic skin for detection of breath, among several other physiological parameters. [31] By using wet transfer process, the authors can transfer the graphene strain sensors from paper onto any object or body part. Respiration rate can be monitored in real-time by attaching the sensor on a mask, philtrum, or the throat.

Finally, Tao *et al.* developed a pressure sensor based on LIG, where the graphene foam is directly patterned onto a polyimide substrate with an infrared laser. Using this methodology, the authors obtained a dual-functional electronic skin (E-skin) to monitor the sleep apnea and alarm once the is hold for more than 10 s. [64] The gauge factor of the device, equal to 316.3, indicates ultra-high sensitivity and permits even the detection of the weakest physiological signals.

Besides wearable pressure/strain sensors, humidity sensors are a valid alternative for respiratory rate monitoring. Such devices measure the difference in relative humidity (RH) between exhala-

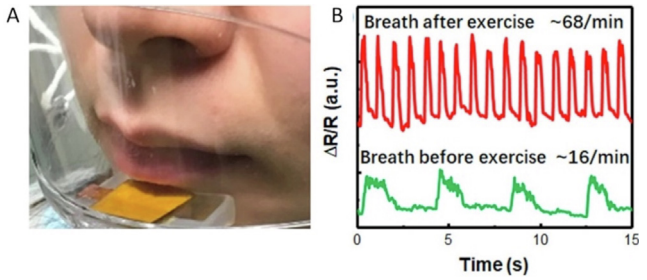

Fig. 8. Sensors for monitoring respiration are highly valuable to monitor physiological signals in hospitalized patients. For such a use, pressure sensors are widely investigated: (a) Application for respiration detection using a GO-coated tissue paper. (b) Response curves for breathing before and after exercise. Reproduced from ref. [63], Copyright 2017 American Chemical Society.

tion and inhalation, since the exhaled airflow has higher RH compared to ambient air. Based on this concept, various humidity sensors based on 2D materials were developed. GO is the most widespread 2D material to design humidity sensors, due to its elevated surface area and superpermeability to water molecules. Furthermore, GO surface functional groups in contact with water can generate protons, producing a detectable decrease in the electrical impedance of the material. [118] For example, a wireless humidity sensor to monitor respiratory rate based on poly(dopamine) and graphene oxide has been reported by He *et al.* [65] In this device, the humidity sensing mechanism is based on the constant formation and breaking of hydrogen bonding between poly(dopamine) and water molecules. The resulting sensor allows to discern among slow, medium, and rapid breathing states, as well as record the real-time respiratory signal during outdoor exercise, with high sensitivity, ultrafast response, and reduced hysteresis (Fig. 9). Ren *et al.* also developed a humidity sensor for respiration monitoring based on porous graphene, GO, PEDOT: PSS and Ag colloids. [66] The as-prepared sensors were used to detect different breathing patterns, being able to distinguish between normal and deep respiration.

Guo *et al.* demonstrated that WS_2 films, synthesized by sulfurization of tungsten, exhibited excellent humidity sensing performance both in flat and flexible substrates. [67] Upon increases of humidity content, the conductivity of the material increases, providing a rapid response in a timeframe of seconds. By depositing WS_2 on graphene electrodes supported on thin and flexible PDMS substrate, a stretchable and wearable humidity sensor was manufactured. The good sensing performance of the device allowed mask-free and real-time monitoring of human respiration rate.

The exhaled human breath is constituted by more than 3,500 components, including an elevated number of volatile organic compounds (VOCs) such as acetone, methanol, ethanol, ammonia, isoprene, isopropanol toluene and several inorganic and sulfur containing gasses. These volatile compounds can also be used as biomarkers for non-invasive diagnosis of diseases. The development of highly sensitive and selective sensors is required to detect these compounds in the part-per-million (ppm) or even part-per-billion (ppb) range and to be able to differentiate healthy from unhealthy conditions. 2D materials have huge potential for the design of gas sensors and have been investigated for the detection of volatile species in breath. Graphene, rGO and BC_6N were used to detect NO_x, a biomarker for lung oxidative stress and inflammation in asthma. [68,69] Graphene can be as well used for the detection of acetone in breath, that is correlated with the glucose levels in blood in diabetic patients. [70] As well, MXenes are under investigation for the detection of VOCs, such as alcohols acetone, toluene, xylene and NH_3. [119] However, all these works described offline

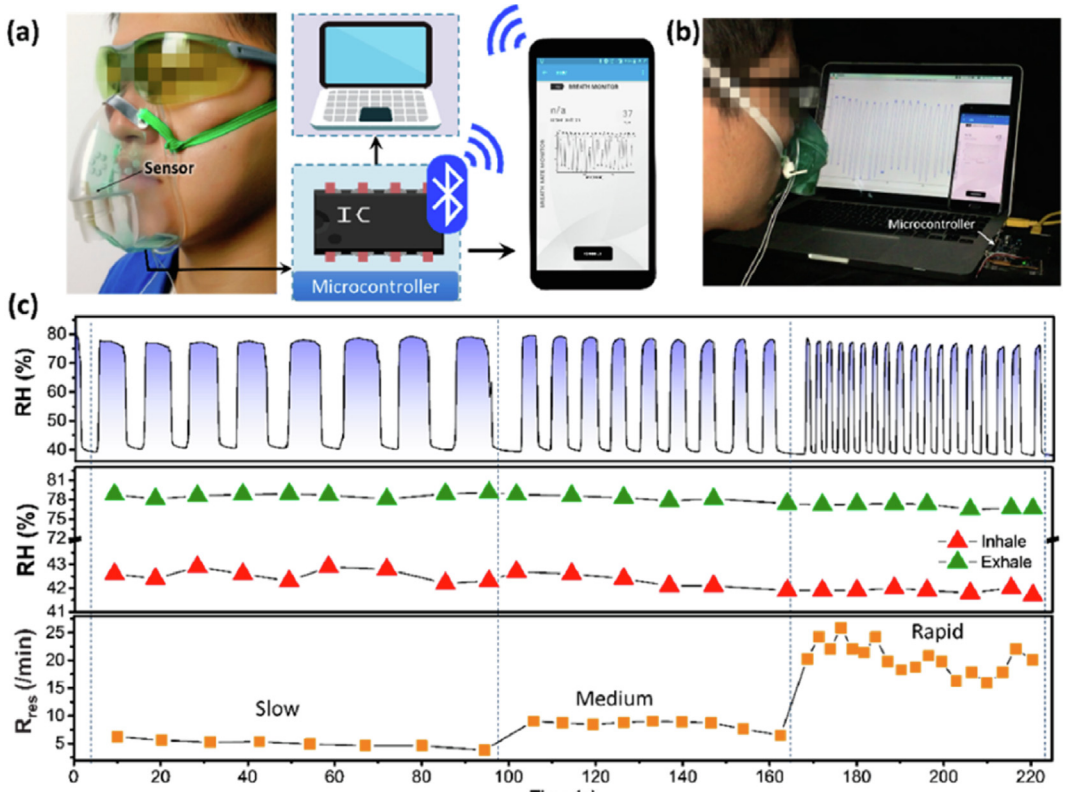

Fig. 9. Humidity sensors are an efficient alternative to monitor human respiratory rate. (a) Photograph and schematic illustrations of the wearable human respiratory monitoring device proposed by He *et al.* (b) Photograph of the wearable device used for in real-time monitoring of human patient. (c) Respiration signal recorded in three breathing states (slow, medium, and rapid), the corresponding exhaled and inhaled air RH values and respiratory rate R_{res}. Reproduced from ref. [65], Copyright 2017 American Chemical Society.

detection of the devices, and 2D materials have not been integrated yet in wearable devices for in real-time chemical analysis of breath.

Human saliva is another attractive corporal fluid for non-invasive diagnostics and monitoring, since it contains several biomarkers, *e.g.*, glucose, lactate, phosphate, hormones, proteins, and antibodies. The concentration of such biomarkers can be correlated to several diseases: cortisol and amino acids have been identified to be indicative of physical and psychological stress; antibodies are useful for the diagnosis of infectious diseases such as HIV and intestinal infections; some protein and mRNA in saliva were also identified as cancer biomarkers. [120] However, a major part of the investigation is conducted through *ex vivo* sensing and just few examples of wearable/implantable graphene-based sensors exist. The most renown example was reported by Mannoor *et al.*, who developed a salivary bacterium sensing platform wearable on the tooth enamel (Fig. 10). [71] A graphene interdigitated electrode was functionalized with antimicrobial peptides to selectively bind bacteria in saliva. Upon binding the analyte, the electrical resistance of the device is altered allowing the quantitative detection of bacteria. The graphene sensor was printed on a water-soluble silk substrate to allow the easy transfer on the tooth enamel. Furthermore, the authors integrated an inductive coil antenna in the device to allow wireless readout. Apart from bacteria detection, the proposed device was used as well for real-time monitoring of respiration.

Finally, a graphene sensor was also used to monitor swallowing in patients subjected to cancer post-radiation therapy, who might present reduced swallowing activity and dysphagia. [72] The sensor is a wearable piezo-resistor made of palladium nano-islands on single-layer graphene placed on the submental region. The differences in swallowing activity between no dysphagic and dysphagic patient can be detected monitoring the tensile and compressive strain of the device. Dysphagic patients took significantly longer time to swallow the bolus compared to no dysphagic ones. This sensor, when combined with a machine-learning algorithm, can be used to monitor patients in real-time, while discerning among signals due to coughing, turning of the head, and swallowing of boluses of different consistencies.

4. Wearable and implantable ocular sensors

Fundamental parameters to consider during the design of eye implantable and wearable sensors are the softness and mechanical properties of the optoelectronics, which must match those of the eyes, particularly for long term ocular prosthesis. Good flexibility of the device is another essential factor, since the devices must perfectly adapt to the hemispherical curvature of the eye and the retina. Moreover, to avoid interferences with the wearer vison, electronics are required to have reduced opacity. 2D materials possess several of the fundamental properties required for eye implants such as: electrical conductivity, flexibility, reduced interfacial traction, biocompatibility, and transparency.

Within the most diffused eye wearable devices, contact lenses equipped with sensors can provide a non-invasive and continuous detection of metabolites in tears. Among various biomarkers that can be detected with smart contact lenses, glucose is particularly important for the diagnosis and monitoring of diabetic patients. Kim *et al.* reported a transparent and stretchable sensor, integrated in soft contact lenses for the wireless detection of glucose. [11] The fundamental component of the sensor is a gFET, a CVD graphene film deposited on metal nanowires contact, providing a transparent, stretchable, and flexible electronic. The gFET has been modified with glucose oxidase (GOD) to enable the selective sensing of glucose. The enzyme was immobilized using 1-pyrenebutanoic acid succinimidyl ester, which interacts with graphene through π-π interactions. The authors integrated the device with a resistance, an inductance, a capacitance and a radiofrequency circuit, demonstrating the feasibility of in real-time and *in vivo* glucose detection on a rabbit eye. The glucose detection with wearable contact lenses was further improved by Park *et al.* in 2018. [12] The authors enhanced the operational stability and sensitivity of gFET sensing devices, by co-immobilizing catalase and GOD enzymes on the transistor. The catalase is used to perform a cascade reaction, to decompose the H_2O_2 produced by the GOD, whose continues production and accumulation can degrade the enzymatic activity of GOD. Furthermore, a light-emitting diode (LED) was integrated in the contact lens to automatically display the real-time glucose concentration, warning the user if the recommended threshold is exceeded.

Glucose in not the only metabolite that can be detected using wearable contact lenses. Jang *et al.* reported an integrated system for in real-time, remote monitoring and therapy of chronic ocular surface inflammation (OSI). [13] The device consists of a soft, smart contact lens for the diagnosis combined with an eyelid heat patch for hyperthermia treatment. A gFET was integrated in the contact lens to perform quantitative analysis of matrix metalloproteinase-9 (MMP-9) in tears, a known biomarker for OSI diagnosis. The gFET was obtained by transferring CVD graphene onto a network of silver nanowires, supported on the contact lens. To achieve selectivity toward MMP-9 the graphene surface was functionalized with antigen binding fragments (Fab) of immunoglobulin G (IgG). Once again, the receptors were immobilized on gFET using 1-pyrenebutanoic acid succinimidyl ester. A wireless therapeutic device, consisting in a stretchable and transparent eye patch was combined with the sensing platform. Due to the presence of a continuous silver nanofibers network this patch was able to warm the upper and lower eyelid, facilitating the lipid expression of the meibomian gland and therefore reliev-

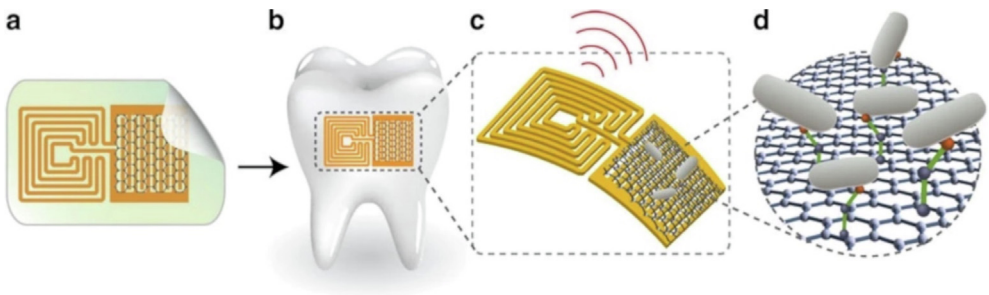

Fig. 10. Human saliva is also considered a very rich biofluid for non-invasive diagnosis and monitoring of human health through chemical sensing of specific biomarkers: (a) Graphene-based bacteria interdigitated electrode printed onto bioresorbable silk, developed by Mannoor *et al.* (b) Transfer of the sensor onto the surface of a tooth. (c) Schematic representation of the sensor, illustrating the wireless readout. (d) Interaction of the pathogenic bacteria with the peptide's receptors on the graphene interdigitated electrode. Reproduced from ref. [71], Copyright 2021 Elsevier.

ing the symptoms of OSI. Both diagnostic and therapeutic devices were incorporated through wireless communication enabling automated hyperthermia treatments based on the signals detected from the contact lens.

Another significant indicator that can be acquired from human eyes is intraocular pressure (IOP). Elevated IOP is a physiological condition which increase the risk of glaucoma, a leading cause of human blindness. Graphene can be used as a strain sensor for IOP continuous monitoring. [11] Liu *et al.* demonstrated that graphene nano-walls, a thin film of wrinkled graphene, can be used as strain sensor integrated in a contact lens for non-invasive IOP monitoring. [73] The contact lens was tested *ex vivo* on porcine eye. Due to their elevated Gauge Factor (3 orders of magnitude higher in respect to metals), graphene nano-walls presented a detection sensitivity higher compared to previously published wearable devices for IOP monitoring.

Apart from tear's biomarker sensing, 2D materials can be used as well to manufacture artificial retinas. The biological synapses, present in the retina, have a light evoked excitatory and inhibitory behavior, a key for the image sensing and recognition. This means that, when synapses are exposed to a light pulse, a post-synaptic current is generated. Some 2D materials, such as MoS_2 and 2D perovskite, present a similar behavior, being able of transducing light pulses in electrical signal and functioning as artificial synapses. In this optic, Chansoon *et al.* proposed an implantable, human eye inspired, soft optoelectronic device based on ultrathin CVD MoS_2 and graphene films. [5] The device consisted in a hemispherical curved image sensor (CurvIS) that allows obtaining aberration free imaging and a wide field of view (Fig. 11). MoS_2 is a promising photoadsorbing component for CurvIS, due to its elevated photoabsorption coefficient, photoresponsivity, high fracture strain, softness, and ultrathin thickness. The optoelectronic consists in a phototransistor array composed of MoS_2-Graphene heterostructure and other nanomembranes, *e.g.*, dielectric Al_2O_3, Ti/Au gate and Si_3N_4 substrate incapsulated in a polyimide film (Fig. 11). The ultrathin thickness of the device, less than 900 nm in total, dramatically decreased the bending strain. Under illumination, the MoS_2 devices generated a photocurrent that is proportional to the incident light intensity. A further advantage was that the captured image was not affected by the IR radiation due to IR blindness of the MoS_2-based phototransistor, originating from material bind gaps. By using this ultrathin CurvIS, the authors were able to capture various images, demonstrating the feasibility of the device as artificial retina. The CurvIS was implanted in rat's eyes and interfaced with a neuronal recording system. Both the short (1 week) and long (9 week) biocompatibility of the implant was assessed monitoring the expression of the fibroblast growth factor 2 and fibrillary acidic protein, both comparable with the control group. The electrode attached on the retina successfully stimulated the optic nerves, whose excitation was monitored by penetrative electrodes implanted in the visual cortex. When the rat eye was exposed to pulsed optical signals, the artificial rat retina sensed the intermittent light. This information was therefore transmitted to the visual cortex via optic nerves and recorded as elicited spikes.

Other materials that could be employed as artificial synapses are 2D perovskite and MXenes, [121-123] which, thanks to their peculiar structure and properties, were successfully employed to develop UV-photodetectors. Unless the implementation of photodetectors as wearable devices was widely investigated in the recent years, [124] there are only few examples of broadband photodetector activated by visible light. [121,125] For this reason, the application of these materials as an implantable artificial retina has not been yet achieved.

5. Implantable neurological sensors

In the recent years, graphene-based electronics were widely applied in the development of innovative neural interfaces. Active implantable or wearable devices are promising tools to achieve a better understanding of brain functionality as well as diagnosis and treatment of several neurodegenerative diseases. Electronic devices working within the nervous system can be mainly used for the recording electrophysiological signals, stimulation of the surrounding tissue and sensing different biomarkers, as neurotransmitters. Depending on the desired application, a different kind of positioning is necessary: the device can be placed externally on the scalp, close to the dura mater for recording global brain activity or implanted within the cortex to obtain better spatial and temporal resolution of the signals. [126].

In addition, neural implants need to fulfil some important requirements: i) wide operating range able to record signals from single neuron (tens of μV) to neuron assemblies action potentials (hundreds of μV); [126] ii) stimulating charge injection capacity within the effective and the safety limits (10–800 $\mu C \cdot cm^{-2}$); [29] iii) biocompatibility and durability; iv) low induction of foreign body response and subsequential encapsulation. Considering all these points, graphene-based materials emerged as promising candidates to build new neural interfaces that combine features as flexibility and transparency with suitable electronic properties and good biocompatibility.

Graphene neural implants can be classified in two subclasses: electrodes and transistors. As a first example, in 2016 a carbon fiber microelectrode modified with electropolymerized PEDOT/-graphene oxide composite was used for real-time monitoring of dopamine by means of fast scan cyclic voltammetry in mice brain with high sensitivity and response rate. The introduction of PEDOT/graphene oxide composite not only increases the surface area, but also aids actively the detection. Indeed, the presence of graphene oxide allows the adsorption of the oxidation quinone containing products, shown to be able to catalyse the dopamine-electrode electron transfer, this resulting in a significative enhancement of the dopamine LOD. [74].

A general trend in the development of both electrode and transistor-based electronics is moving from single device to multidevice arrays architectures to enhance the spatial and temporal resolution of the devices. Multielectrode and multitransistor arrays were successfully applied to electrophysiological signals monitoring, both having their pros and cons. As an example, simultaneous recording and stimulation of mice brain was achieved using 16-channel electrodes flexible array. This device, composed of 4-layers graphene supported on flexible Parylen C, showed low charge injection capacity, suitable for the safe stimulation of the mice brain and representing a promising tool for neurodegenerative disease treatment. In addition, the transparency of the platform allows the simultaneous recording and fluorescence calcium imaging (Fig. 12). [29].

Similarly, Lu and co-workers [127] developed a multichannel architecture based on porous graphene foam synthesized by laser pyrolysis deposited onto flexible polyimide. This three-dimensional electrode array was applied to recording and stimulation of the motor cortex, showing suitable charge injection capacity and low SN ratio. Thanks to the large area of the devices, it was possible to precisely localize the cortex area associated with the leg motion of the ankle and knee flexion, thus proving the power of these electronics in high resolution brain mapping.

By means of multichannel devices it is also possible to simultaneously monitor electrophysiological and chemical signals. In 2016 Liu *et al.* [75] employed a reduced graphene oxide-gold oxide (rGO/Au_2O_3) nanocomposite multielectrode array as neural probe to

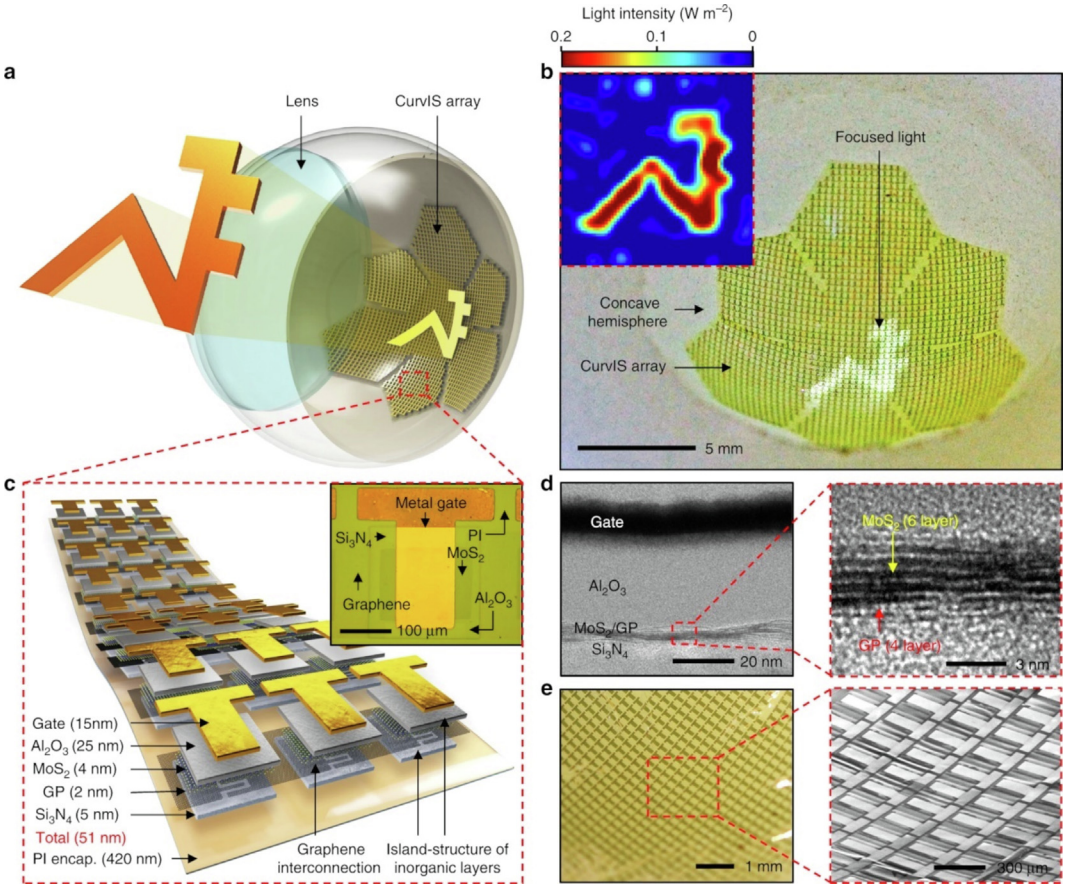

Fig. 11. MoS_2 optoelectronic properties allow to manufacture artificial retinas, with ability to transduce light pulses in artificial synapses. In this example, a CurvIS array based on MoS_2-graphene heterostructure is described. (a) Schematic illustration of the CurvIS. (b) Optical image of the device. In the inset is shown the image captured by the CurvIS array. (c) Schematic illustration of the layered structure of the device. In the inset is represented an optical microscope image of a single phototransistor. (d) Transmission electron microscope image of the MoS2-graphene phototransistor cross-section. (e) Optical (left) and magnified scanning electron microscope (right) image of the high-density CurvIS array mounted on the concave hemisphere. Reproduced from ref. [5], Copyright 2017 Nature.

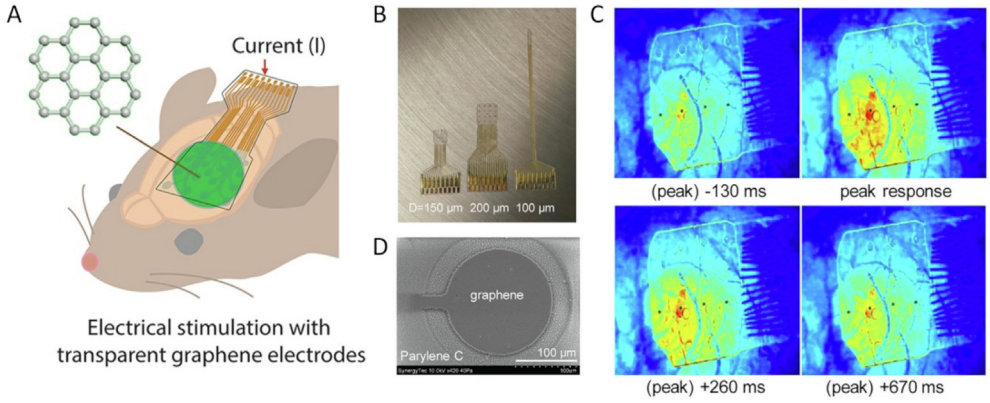

Fig. 12. Graphene electrodes have been widely applied as neural interfaces. Multidevice arrays are preferred as they offer a higher resolution and spatial recording. In this example, a 16-channel flexible array is shown: (a) Representation of multielectrode array implantation over motor cortex for electrical stimulation in mice model; (b) Three different kind of neural probes. (c) SEM image of graphene electrode. (d) Calcium imaging fluorescence visualization of the intensity of neural response at different time points. Reproduced from ref. [29], Copyright 2018 American Chemical Society.

detect H_2O_2 produced during ischemic cascade in rat model. The device showed a good selectivity toward the target analyte detected by chronoamperometry at −0.5 V, testing common interferents as glucose and dopamine, as well as fast response and low limit of detection. In addition, the power of this architecture lays in the possibility to further validate the functional neuronal changes by recording neural evoked potentials characteristic of ischemic stroke.

The main drawback of microelectrode array is that electrode impedance and noise increase when the electrode area decreases. [76] Thus, a compromise between noise and spatial resolution must be found. In this context, microtransistor arrays have the

advantage of intrinsic amplification capability leading to less sensitivity to external noise. In addition, transistors performances are stable upon downscaling, [77] this allowing manufacturing of high-density multichannel devices for high resolution mapping. These devices are usually composed by CVD graphene as it shows high carrier mobility, wide electrochemical window and electrochemical inertness, compatibility with biological fluids and high surface area. [77].

These versatile devices were applied to different kind of recordings, including the pre-epileptic and visual evoked activity detection [76] and infraslow cortical brain activity below 0.1 Hz, usually associated with stroke and brain injury. [77] In both studies, graphene devices showed higher SN ratio compared to state-of-the-art platinum electrodes, consequence of the intrinsic amplification capability of the graphene architecture. In addition, the transistor design gave the possibility to tune the device response by optimizing the best bias for each signal.

Although the great features of transistor bioelectronics as amplification capability and low sensitivity to environmental interferences, there is still a lack of transistor-based biosensors applied *in vivo*. Compared to graphene electrodes, which can intrinsically recognize electroactive molecules, transistor-based biosensors always need a specific receptor. Thus, the main issue in biosensors development is immobilizing specific receptor onto graphene while preserving the electronic properties of the transistor. Indeed, graphene-based transistor performances are dramatically affected by disruption of graphene lattice, making many modifications route unfeasible. In this sense, a required step to achieve the development of the next generation neural sensors is the implementation of new mild functionalization strategy to anchor *in vivo* stable receptors, as aptamers, preserving the functionality of the device.

Finally, it is worth mentioning that in the recent years the study of other 2D materials as metal dichalcogenides has spread rapidly also exploring their biological applications. As an example of *in vivo* sensing using metal dichalcogenides, in 2018 an interdigitated electrode geometry based on MoS_2 was employed to create a pressure, temperature and strain sensor to be used for brain monitoring. [78] Composed of a sandwich of different materials as silicon oxide and poly(lactic-co-glycolic acid) protecting the electrodes by biofluids interference, the sensor is capable to sense different physiological parameters by monitoring the electrode resistivity once implanted intracranially. In addition, due to the bioabsorbable nature of all the components, the sensor disappeared within 2 months from implantation, making it suitable for temporary monitoring of brain injuries.

6. Implantable cardiovascular sensors

Diseases related to the cardiovascular system are among the most frequent and the major cause of death worldwide. The engineering of reduced size electro-responsive devices, able to ubiquitously monitor the cardiovascular activity, is essential not only for the early diagnosis of cardiovascular diseases, but also to reduce healthcare costs. [128-131] However, the development of implantable systems for *in vivo* sensing in the cardiovascular system is extremely challenging. In fact, blood is the most complex among the biological fluids, compared, for example, to saliva or sweat, because of its highly diverse biological composition and because it is where the response to external agents is more active. [95,132] Most likely, a sensor implanted in the circulatory system is soon recognized by cells of the immune system and interacting with several plasma proteins, ending surrounded by a fibrous matrix containing metabolically active cells, *i.e.*, activated platelets. All of this is a potential health risk, but also affect the sensor environment and its performance in terms of reliability, sensitivity and specificity. The employment of certain type of coatings, *e.g.*, poly (ethylene glycol) (PEG), poly(sulfobetaine methacrylate) (pSBMA), or poly(carboxybetaine methacrylate), is a very intensely studied approach to reduce protein absorption and improve blood-compatibility of sensors, although the challenge in this field is still very high. [132].

In 2013, Yao and co-workers developed a graphene-based microprobe by microelectromechanical system technology, able to record an ECG when in contact with the heart of a zebrafish. [79] This device combines CVD graphene as electrode and SU-8 as flexible and biocompatible substrate, followed by a coating with PDMS. Interestingly, they increased the graphene hydrophilicity by mild steam plasma (SP), useful to introduce hydroxylic groups, and observed that this step was necessary to record a proper ECG with the typical P, QRS and T wave pattern for the heart of zebrafish.

More recently Xue and co-workers employed rGO as main component to develop coaxial heterogeneous microfibers for *in vivo* pressure detection (Fig. 13). [32] Cold direct pen writing method [133] has been employed to obtain rGO microfoam of reduced size, essential for *in vivo* application. The microfiber contains a core of low density rGO aerogel (600 mm diameter) linked to an outer shell of high-density rGO-polypyrrol (rGOPPy) aerogel shell (100 mm thick). Core and shell were bridged by regularly arranged monolithic rGO nanosheets. The final formulation presented an ultrahigh sensitivity of 18.27 kPa^{-1} in the pressure range of 20–40 Pa, high resolution of 0.2 Pa, and good stability for 450 cycles. The microdevice has been implanted onto the heart of a mice and was able to convert the pressure derived from the heartbeat into electrical signal in real-time.

7. Other graphene-based implantable devices

Apart from the organs described above, there are few other worth mentioning examples of graphene-based devices implantable in the muscular tissues, ears, or intestinal tract.

Kim *et al.* introduced a stretchable and transparent sensor/actuator for the simultaneous recording of EMG and performing electrical muscle stimulation. [30] EMG is fundamental for electrodiagnosis of many motion-related neuromuscular diseases, while electrical muscle stimulation is a promising procedure to enhance and recover the strength and function of skeletal muscles. The device proposed by the authors was composed of a cell-sheet–graphene hybrid, an aligned C2C12 myoblast sheet, integrated on buckled, Au-doped, and mesh-patterned graphene electrodes, which was mounted on a submicron thick polyimide membrane and a soft PDMS substrate. This electrode served as a smart cell culture substrate, able to control aligned proliferation and differentiation of muscle cells *in vitro*. *In vivo*, when implanted onto the hind limb skeletal muscle region of mice, allows to record electromyographical signals, and stimulate implanted sites electrically and/or optically.

Furthermore, CVD graphene has been integrated, as well, in cochlear implants. [6] In this device, graphene was used as a conductive neural interface able to transduce the electric-acoustic stimulation into action potentials. Moreover, the presence of graphene allows to grow phenotypically healthy and physiologically functioning spiral ganglion neurons (SGNs), which are the targeted of the cochlear implant.

Lee *et al.* present a multifunctional endoscope-based interventional system that integrates transparent bioelectronics, based on graphene, in combination with radio frequency ablation therapy with theragnostic nanoparticles, which are photoactivated within highly localized space near tumors (Fig. 14). [14] These advanced electronics and nanoparticles collectively enabled optical

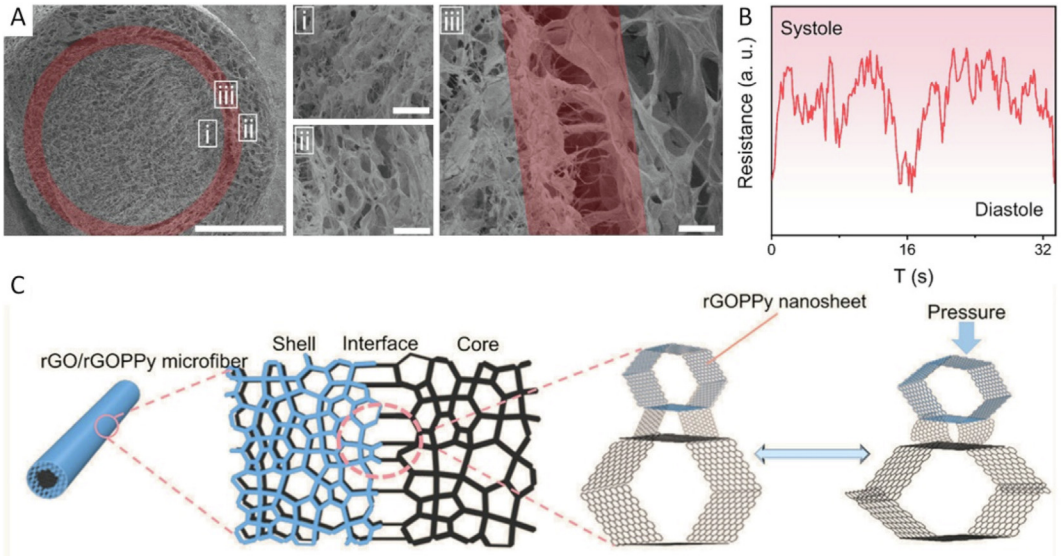

Fig. 13. Pressure sensors with reduced size are required for cardiovascular monitoring and early diagnosis of related diseases. In this example, Xue *et al* developed a high sensitive sensor mainly composed of GO: (a) SEM micrograph of the cross section of the porous rGO/rGOPPy microfiber at the base of the heart-implantable strain sensor. (b) Resistance signal of the sensor implanted on the mice heart. (c) Schematic representation of the rGO/rGOPPy microfiber structure. Reproduced from ref. [32], Copyright 2021 American Chemical Society.

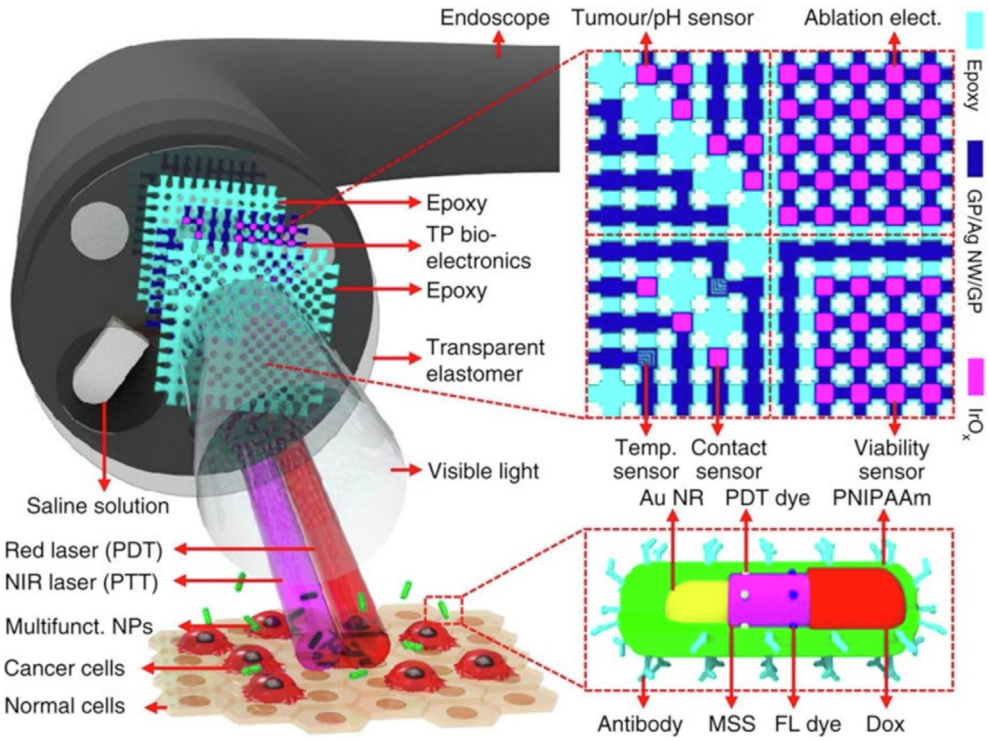

Fig. 14. Schematic illustrations of multifunctional graphene-based endoscope based on transparent bioelectronics and theragnostic nanoparticles. Reproduced from ref. [14], Copyright 2015 Nature.

fluorescence-based mapping, electrical impedance and pH sensing, contact/temperature monitoring, radio frequency ablation and localized photo/chemotherapy, as the basis of a closed-loop solution for colon cancer treatment. *In vitro*, *ex vivo* and *in vivo* experiments highlighted the utility of this technology for accurate detection, delineation and rapid targeted therapy of colon cancer or precancerous lesions. The graphene based transparent electronic provided impedance- and pH-based sensing, facilitating the localization of colon cancers. Additionally, mechanical contacts and temperature sensors provide physiological sensing during cancer detection and treatment. The transparency of the electronic device enables the integration of several sensing and therapeutic components on the tip of the endoscope without blocking the field of vision of the camera or the light. Theragnostic gold nanoparticles

can be delivered locally and used as phototherapeutic and chemotherapeutic agents, activated with light. Such synergistic effects between the transparent bioelectronics and theragnostic NPs can enhance the tumor detection accuracy and the efficiency of the treatment.

8. Conclusions

2D materials are ideal candidates for the manufacturing of miniaturized, flexible, and transparent electronics and are gaining increasing importance in the design of wearable or implantable biosensors. In the last years a huge number of works demonstrated the application of graphene-related materials in real time and *in vivo* monitoring of multiple physiological parameters. These materials were applied as efficient transductors in a vast number of devices monitoring pressure, humidity, sound, light, body movement, respiration, heart rate, ECG, EMG, EEG, speech vibration, intraocular pressure, biomarkers, and bacteria concentration, among others.

Graphene has been the most investigated 2D material for wearable and implantable devices, and the farthest along the pathway from research to clinical adoption. However, other 2D materials, such as TMDs, MoS_2, Mxenes and perovskites are rapidly filling the gap. These materials have properties such as piezo resistivity and photocurrent generations that are missing in graphene materials, making them interesting candidates for the manufacture of improved phototransistors or gauge devices.

Owing to the interest of huge industrial players, the field of wearable/implantable devices for the monitoring of physiological signals is expected to grow fast in the next years. Several are the 2D materials-based prototypes in the pipeline. Nevertheless, these products are still in pre-clinical trials and are foreseen to be market-ready in five to ten years.

Various are the main obstacles hampering the clinical and commercial development of 2D material-based sensors. In first instance, the application of these devices requires clinical approval by rigorous regulatory authorities, which are often concerned about the potential toxicity of new materials. [89] Furthermore, attention should be paid to the long-term stability of 2D materials in biological environments. In the case of electrochemical electrodes, salt solutions may penetrate the passivating active surface, inducing redox reactions that may cause the degradation of 2D materials. Moreover, the high electric fields applied across the atomically thin layers can cause changes in the material fine structure and alter the ion current. The reproducibility, related to 2D materials manufacturing still needs to be improved. CVD is a promising technique to prepare high quality graphene at industrial level. Nevertheless, uniform large areas of monolayer graphene are difficult to achieve. [134] In addition, subsequent transfer processes can decrease the quality of the 2D material preventing the proper function of the final device. Moreover, the incorporation of the 2D material in the traditional microfabrication process is still problematic. It is imperative to optimize the interface between the graphene device and the flexible electronic to achieve both body adaptation and signal quality. Fully integrated wearable and implantable devices, in addition to high-quality sensors, also require integrated circuits, radio frequency hardware, and power sources, to accomplish efficient communication and powering. Advanced solutions that can transfer, convert, and store energy more efficiently are highly desirable to answer to power-hungry operation performed by the devices. Finally, diagnostic applications based on innovative detection mechanisms require proof-of-concept studies and validation, by comparing them with the current clinical standards. Therefore, extensive clinical studies are required to validate the accuracy and reliability of these systems.

On the basis of these considerations, the use of 2D materials in this field is to date still far from real-world applications and more efforts are still needed to replace traditional bioelectronic with 2D materials.

For these reasons, non-invasive sensors, mainly skin wearable sensors, are currently the most promising technology to detect the physiological signals in real time. These devices are less invasive, with reduced toxicological risks, and are subjected to less strict regulatory requirements. To date, graphene-based wearable sensors are the most advanced in the pathway toward clinical adoption. In this promising field, the efforts should be now focused in solving the drawbacks that hamper the commercialization of these devices, *e.g.,* long term stability, robustness to stress and strain and achieve low cost and scalable production.

In medium-long term, it is possible to foresee the application for nerve tissue sensors, in particular implantable devices in brain, where graphene and 2D materials play a leading role in the efforts toward wider clinical adoption of bioelectronics and electroceuticals. This kind of brain-electronic interfaces is crucial for the diagnosis and the treatment of neural disease, to develop human–machine interaction, and brain-computer interfaces. [126] However, for implantable devices, several challenges, such as biocompatibility, biofouling, as well as power supply, must be solved yet. Several efforts are still required to evaluate the biocompatibility of the devices once implanted. In this frame, we believe that a clear and universal protocol should be assessed to univocally evaluate the immune responses after implantation. This step is crucial not only to prevent medical threats, but also to avoid the risks of errant data, which affect the validity of the monitoring. In fact, adverse response of the organism after the implantation can induce abnormal concentrations of the analytes or modifications in the monitored physiological parameters. Finally, the long-term operational stability must be carefully evaluated as the implanted sensors could be easily fouled by biopolymers present in blood and biological fluids, or covered by glial scars, reducing in this way the lifetime of the device.

Regarding future perspectives, we believe that biodegradable electronics is an exciting line of research, with an immense potential for implantable applications. 2D materials show promising preliminary results in this direction, being able to degrade in a controlled manner without secondary surgery or risk of infection. For example, Cheng et al. have reported a bioabsorbable and multifunctional MoS_2-based sensor for intracranial monitoring of pressure, temperature, strain, and motion in animal models. [126] Preliminary studies suggest that the MoS_2 monolayer is a biocompatible semiconductor, which can be completely dissolved in biofluids after more than two months. Notwithstanding these exciting results, further studies on biocompatibility, degradation process and environmental stability of these new materials are still needed.

Another interesting direction worthy to explore concerns the design of multiparameter sensors. Frequently the analysis of single biomarkers or signals is insufficient to reach an accurate diagnosis. In several cases, sensing of multiple parameters is required to achieve a precise and early diagnosis such as in case of neurological diseases or sepsis. In sport, multiparameter sensing is also highly desirable, allowing to monitor simultaneously different physical and chemical parameters in a user-friendly fashion. [135] Apart from the previously described technical challenges, the miniaturization of the devices becomes fundamental for multiparameter sensors, since few cm^2 must include several sensors (often based on different electronics and sensing mechanisms), with relative communication modules and power supply, avoiding interferences between the components. [135] However, sensors able to simultaneously detect temperature, pH, pressure, and molecular concentra-

tions are highly desirable as they would become portable multifunctional devices for a comprehensive healthcare monitoring.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] D.C. Klonoff, Continuous glucose monitoring, Diabetes Care. 28 (2005) 1231–1239.
[2] F. Van de Werf, D. Chair, A. Ardissino, D.V. Betriu, E. Cokkinos, K.A.A. Falk, D. Fox, M. Julian, F.J. Lengyel, W. Neumann, C. Ruzyllo, S.R. Thygesen, A. Underwood, F.W.A. Vahanian, W. Verheugt, Wijns, Management of acute myocardial infarction in patients presenting with ST-segment elevation, Eur. Heart J. 24 (2003) 28–66, https://doi.org/10.1016/S0195-668X(02)00618-8.
[3] S. Zhang, Y. Song, M. Wang, G. Xiao, F. Gao, Z. Li, G. Tao, P. Zhuang, F. Yue, P. Chan, X. Cai, Real-time simultaneous recording of electrophysiological activities and dopamine overflow in the deep brain nuclei of a non-human primate with Parkinson's disease using nano-based microelectrode arrays, Microsystems Nanoeng. 4 (2018) 17070, https://doi.org/10.1038/micronano.2017.70.
[4] A.H. Furberg, C.B. Ambrosone, Molecular epidemiology, biomarkers and cancer prevention, Trends Mol. Med. 7 (11) (2001) 517–521, https://doi.org/10.1016/S1471-4914(01)02162-1.
[5] C. Choi, M.K. Choi, S. Liu, M.S. Kim, O.K. Park, C. Im, J. Kim, X. Qin, G.J. Lee, K.W. Cho, M. Kim, E. Joh, J. Lee, D. Son, S.H. Kwon, N.L. Jeon, Y.M. Song, N. Lu, D.H. Kim, Human eye-inspired soft optoelectronic device using high-density MoS2-graphene curved image sensor array, Nat. Commun. 8 (2017) 1664, https://doi.org/10.1038/s41467-017-01824-6.
[6] R. Guo, X. Ma, M. Liao, Y. Liu, Y. Hu, X. Qian, Q. Tang, X. Guo, R. Chai, X. Gao, M. Tang, Development and application of cochlear implant-based electric-acoustic stimulation of spiral ganglion neurons, ACS Biomater. Sci. Eng. 5 (12) (2019) 6735–6741, https://doi.org/10.1021/acsbiomaterials.9b0126510.1021/acsbiomaterials.9b01265.s001.
[7] M. Park, Y.J. Park, X. Chen, Y.-K. Park, M.-S. Kim, J.-H. Ahn, MoS2-based tactile sensor for electronic skin applications, Adv. Mater. 28 (13) (2016) 2556–2562, https://doi.org/10.1002/adma.201505124.
[8] V.K. Sangwan, M.C. Hersam, Neuromorphic nanoelectronic materials, Nat. Nanotechnol. 15 (7) (2020) 517–528, https://doi.org/10.1038/s41565-020-0647-z.
[9] C. Schmidt, Bioelectronics: The bionic material, Nature. 483 (2012) S37. https://doi.org/10.1038/483S37a.
[10] A. Ambrosi, C.K. Chua, N.M. Latiff, A.H. Loo, C.H.A. Wong, A.Y.S. Eng, A. Bonanni, M. Pumera, Graphene and its electrochemistry-an update, Chem. Soc. Rev. 45 (9) (2016) 2458–2493.
[11] J. Kim, M. Kim, M.S. Lee, K. Kim, S. Ji, Y.T. Kim, J. Park, K. Na, K.H. Bae, H.K. Kim, F. Bien, C.Y. Lee, J.U. Park, Wearable smart sensor systems integrated on soft contact lenses for wireless ocular diagnostics, Nat. Commun. 8 (2017) 14997, https://doi.org/10.1038/ncomms14997.
[12] 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, J.H. Lee, F. Bien, J.U. Park, Soft, smart contact lenses with integrations of wireless circuits, glucose sensors, and displays, Sci. Adv. 4 (2018) eaap9841, https://doi.org/10.1126/sciadv.aap9841.
[13] J. Jang, J. Kim, H. Shin, Y.G. Park, B.J. Joo, H. Seo, J.E. Won, D.W. Kim, C.Y. Lee, H. K. Kim, J.U. Park, Smart contact lens and transparent heat patch for remote monitoring and therapy of chronic ocular surface inflammation using mobiles, Sci. Adv. 7 (2021) eabf7194, https://doi.org/10.1126/sciadv.abf7194.
[14] H. Lee, Y. Lee, C. Song, H.R. Cho, R. Ghaffari, T.K. Choi, K.H. Kim, Y.B. Lee, D. Ling, H. Lee, S.J. Yu, S.H. Choi, T. Hyeon, D.H. Kim, An endoscope with integrated transparent bioelectronics and theranostic nanoparticles for colon cancer treatment, Nat. Commun. 6 (2015) 10059, https://doi.org/10.1038/ncomms10059.
[15] T. Zhong, J. Li, K. Zhang, A molecular dynamics study of Young's modulus of multilayer graphene, J. Appl. Phys. 125 (17) (2019) 175110, https://doi.org/10.1063/1.5091753.
[16] D. Kuzum, H. Takano, E. Shim, J.C. Reed, H. Juul, A.G. Richardson, J. De Vries, H. Bink, M.A. Dichter, T.H. Lucas, D.A. Coulter, E. Cubukcu, B. Litt, Transparent and flexible low noise graphene electrodes for simultaneous electrophysiology and neuroimaging, Nat. Commun. 5 (2014) 5259, https://doi.org/10.1038/ncomms6259.
[17] V. Georgakilas, J.N. Tiwari, K.C. Kemp, J.A. Perman, A.B. Bourlinos, K.S. Kim, R. Zboril, Noncovalent functionalization of graphene and graphene oxide for energy materials, biosensing, catalytic, and biomedical applications, Chem. Rev. 116 (9) (2016) 5464–5519, https://doi.org/10.1021/acs.chemrev.5b00620.
[18] A. Criado, M. Melchionna, S. Marchesan, M. Prato, The covalent functionalization of graphene on substrates, Angew. Chemie - Int. Ed. 54 (37) (2015) 10734–10750, https://doi.org/10.1002/anie.201501473.
[19] K.F. Mak, J. Shan, Photonics and optoelectronics of 2D semiconductor transition metal dichalcogenides, Nat. Photonics. 10 (4) (2016) 216–226, https://doi.org/10.1038/nphoton.2015.282.
[20] D. Lembke, S. Bertolazzi, A. Kis, Single-layer MoS2 electronics, Acc. Chem. Res. 48 (1) (2015) 100–110, https://doi.org/10.1021/ar500274q.
[21] W.J. Yu, Y. Liu, H. Zhou, A. Yin, Z. Li, Y.u. Huang, X. Duan, Highly efficient gate-tunable photocurrent generation in vertical heterostructures of layered materials, Nat. Nanotechnol. 8 (12) (2013) 952–958, https://doi.org/10.1038/nnano.2013.219.
[22] S. Manzeli, A. Allain, A. Ghadimi, A. Kis, Piezoresistivity and strain-induced band gap tuning in atomically thin MoS2, Nano Lett. 15 (8) (2015) 5330–5335, https://doi.org/10.1021/acs.nanolett.5b01689.
[23] W. Wu, L. Wang, Y. Li, F. Zhang, L. Lin, S. Niu, D. Chenet, X. Zhang, Y. Hao, T.F. Heinz, J. Hone, Z.L. Wang, Piezoelectricity of single-atomic-layer MoS2 for energy conversion and piezotronics, Nature. 514 (7523) (2014) 470–474, https://doi.org/10.1038/nature13792.
[24] P. Suvarnaphaet, S. Pechprasarn, Graphene-based materials for biosensors: A review, Sensors (Switzerland). 17 (2017) 2161, https://doi.org/10.3390/s17102161.
[25] X. Hu, T. Huang, Z. Liu, G. Wang, D.a. Chen, Q. Guo, S. Yang, Z. Jin, J.-M. Lee, G. Ding, Conductive graphene-based E-textile for highly sensitive, breathable, and water-resistant multimodal gesture-distinguishable sensors, J. Mater. Chem. A. 8 (29) (2020) 14778–14787.
[26] Z. Hao, Y. Luo, C. Huang, Z. Wang, G. Song, Y. Pan, X. Zhao, S. Liu, An intelligent graphene-based biosensing device for cytokine storm syndrome biomarkers detection in human biofluids, Small. 17 (29) (2021) 2101508, https://doi.org/10.1002/smll.v17.2910.1002/smll.202101508.
[27] Y.J. Yun, J. Ju, J.H. Lee, S.-H. Moon, S.-J. Park, Y.H. Kim, W.G. Hong, D.H. Ha, H. Jang, G.H. Lee, H.-M. Chung, J. Choi, S.W. Nam, S.-H. Lee, Y. Jun, Highly elastic graphene-based electronics toward electronic skin, Adv. Funct. Mater. 27 (33) (2017) 1701513, https://doi.org/10.1002/adfm.201701513.
[28] Q. An, S. Gan, J. Xu, Y.u. Bao, T. Wu, H. Kong, L. Zhong, Y. Ma, Z. Song, L.i. Niu, A multichannel electrochemical all-solid-state wearable potentiometric sensor for real-time sweat ion monitoring, Electrochem. Commun. 107 (2019) 106553, https://doi.org/10.1016/j.elecom.2019.106553.
[29] D.-W. Park, J.P. Ness, S.K. Brodnick, C. Esquibel, J. Novello, F. Atry, D.-H. Baek, H. Kim, J. Bong, K.I. Swanson, A.J. Suminski, K.J. Otto, R. Pashaie, J.C. Williams, Z. Ma, Electrical neural stimulation and simultaneous in vivo monitoring with transparent graphene electrode arrays implanted in GCaMP6f mice, ACS Nano. 12 (1) (2018) 148–157, https://doi.org/10.1021/acsnano.7b04321.
[30] S.J. Kim, K.W. Cho, H.R. Cho, L. Wang, S.Y. Park, S.E. Lee, T. Hyeon, N. Lu, S.H. Choi, D.-H. Kim, Stretchable and transparent biointerface using cell-sheet-graphene hybrid for electrophysiology and therapy of skeletal muscle, Adv. Funct. Mater. 26 (19) (2016) 3207–3217, https://doi.org/10.1002/adfm.201504578.
[31] Y. Qiao, Y. Wang, H.e. Tian, M. Li, J. Jian, Y. Wei, Y.e. Tian, D.-Y. Wang, Y.u. Pang, X. Geng, X. Wang, Y. Zhao, H. Wang, N. Deng, M. Jian, Y. Zhang, R. Liang, Y.i. Yang, T.-L. Ren, Multilayer graphene epidermal electronic skin, ACS Nano. 12 (9) (2018) 8839–8846, https://doi.org/10.1021/acsnano.8b02162.
[32] Q. Jiang, X. Ma, Y. Chai, H. Ma, F. Tang, K. Hua, R. Chen, Z. Jin, X. Wang, J. Ji, X. Yang, R. Li, H. Lian, M. Xue, Reduced graphene oxide-polypyrrole aerogel-based coaxial heterogeneous microfiber enables ultrasensitive pressure monitoring of living organisms, ACS Appl. Mater. Interfaces. 13 (4) (2021) 5425–5434, https://doi.org/10.1021/acsami.0c19949.
[33] B. Rolfe, J. Mooney, B. Zhang, S. Jahnke, S.-J. Le, Y.-Q. Chau, Q. Huang, H. Wang, G. Campbell, J. Campbell, The fibrotic response to implanted biomaterials: implications for tissue engineering, in: D. Eberli (ed.), Regenerative medicine and tissue engineering - Cells and biomaterials, IntechOpen, London, (2011) 551–568. https://doi.org/10.5772/21790.
[34] C.E. Witherel, D. Abebayehu, T.H. Barker, K.L. Spiller, Macrophage and fibroblast interactions in biomaterial-mediated fibrosis, Adv. Healthc. Mater. 8 (2019) 1801451, https://doi.org/10.1002/adhm.201801451.
[35] F. Lotti, F. Ranieri, G. Vadalà, L. Zollo, G. Di Pino, Invasive intraneural interfaces: Foreign body reaction issues, Front. Neurosci. 11 (2017) 497, https://doi.org/10.3389/fnins.2017.00497.
[36] G. Rong, S.R. Corrie, H.A. Clark, In vivo biosensing: progress and perspectives, ACS Sensors. 2 (3) (2017) 327–338, https://doi.org/10.1021/acssensors.6b00834.
[37] Y. Cai, J. Qin, W. Li, A. Tyagi, Z. Liu, M.D. Hossain, H. Chen, J.-K. Kim, H. Liu, M. Zhuang, J. You, F. Xu, X. Lu, D. Sun, Z. Luo, A stretchable, conformable, and

biocompatible graphene strain sensor based on a structured hydrogel for clinical application, J. Mater. Chem. A. 7 (47) (2019) 27099–27109, https://doi.org/10.1039/C9TA11084D.
[38] S. Chun, W. Son, D.W. Kim, J. Lee, H. Min, H. Jung, D. Kwon, A.-H. Kim, Y.-J. Kim, S.K. Lim, C. Pang, C. Choi, Water-resistant and skin-adhesive wearable electronics using graphene fabric sensor with octopus-inspired microsuckers, ACS Appl. Mater. Interfaces. 11 (18) (2019) 16951–16957, https://doi.org/10.1021/acsami.9b04206.
[39] P. Sahatiya, S. Badhulika, Wireless, smart, human motion monitoring using solution processed fabrication of graphene–MoS2 transistors on paper, Adv. Electron. Mater. 4 (6) (2018) 1700388, https://doi.org/10.1002/aelm.v4.6.
[40] S.J. Kim, S. Mondal, B.K. Min, C.-G. Choi, Highly sensitive and flexible strain–pressure sensors with cracked paddy-shaped MoS2/Graphene foam/ecoflex hybrid nanostructures, ACS Appl. Mater. Interfaces. 10 (42) (2018) 36377–36384, https://doi.org/10.1021/acsami.8b11233.
[41] M. Xin, J. Li, Z. Ma, L. Pan, Y. Shi, MXenes and their applications in wearable sensors, Front. Chem. 8 (2020) 297, https://doi.org/10.3389/fchem.2020.00297.
[42] C.S. Boland, U. Khan, C. Backes, A. O'Neill, J. McCauley, S. Duane, R. Shanker, Y. Liu, I. Jurewicz, A.B. Dalton, J.N. Coleman, Sensitive, high-strain, high-rate bodily motion sensors based on graphene–rubber composites, ACS Nano. 8 (9) (2014) 8819–8830, https://doi.org/10.1021/nn503454h.
[43] J. Ramírez, D. Rodriquez, A.D. Urbina, A.M. Cardenas, D.J. Lipomi, Combining high sensitivity and dynamic range: wearable thin-film composite strain sensors of graphene, ultrathin Palladium, and PEDOT:PSS, ACS Appl. Nano Mater. 2 (4) (2019) 2222–2229, https://doi.org/10.1021/acsanm.9b00174.
[44] Y. Wang, L. Wang, T. Yang, X. Li, X. Zang, M. Zhu, K. Wang, D. Wu, H. Zhu, Wearable and highly sensitive graphene strain sensors for human motion monitoring, Adv. Funct. Mater. 24 (29) (2014) 4666–4670, https://doi.org/10.1002/adfm.201400379.
[45] F. Yin, X. Li, H. Peng, F. Li, K. Yang, W. Yuan, A highly sensitive, multifunctional, and wearable mechanical sensor based on RGO/synergetic fiber bundles for monitoring human actions and physiological signals, Sensors Actuators B Chem. 285 (2019) 179–185, https://doi.org/10.1016/j.snb.2019.01.063.
[46] Y. Pang, K. Zhang, Z. Yang, S. Jiang, Z. Ju, Y. Li, X. Wang, D. Wang, M. Jian, Y. Zhang, R. Liang, H. Tian, Y. Yang, T.-L. Ren, Epidermis microstructure inspired graphene pressure sensor with random distributed spinosum for high sensitivity and large linearity, ACS Nano. 12 (3) (2018) 2346–2354, https://doi.org/10.1021/acsnano.7b0761310.1021/acsnano.7b07613.s001.
[47] J. Yang, K. Zhang, J. Yu, S. Zhang, L. He, S. Wu, C. Liu, Y. Deng, Facile fabrication of robust and reusable pdms supported graphene dry electrodes for wearable electrocardiogram monitoring, Adv. Mater. Technol. 6 (9) (2021) 2100262, https://doi.org/10.1002/admt.v6.910.1002/admt.202100262.
[48] F.J. Romero, E. Castillo, A. Rivadeneyra, A. Toral-Lopez, M. Becherer, F.G. Ruiz, N. Rodriguez, D.P. Morales, Inexpensive and flexible nanographene-based electrodes for ubiquitous electrocardiogram monitoring, Npj Flex. Electron. 3 (2019) 12, https://doi.org/10.1038/s41528-019-0056-2.
[49] S. Kabiri Ameri, R. Ho, H. Jang, L.i. Tao, Y. Wang, L. Wang, D.M. Schnyer, D. Akinwande, N. Lu, Graphene electronic tattoo sensors, ACS Nano. 11 (8) (2017) 7634–7641, https://doi.org/10.1021/acsnano.7b02182.
[50] D. Kireev, S.K. Ameri, A. Nederveld, J. Kampfe, H. Jang, N. Lu, D. Akinwande, Fabrication, characterization and applications of graphene electronic tattoos, Nat. Protoc. 16 (5) (2021) 2395–2417, https://doi.org/10.1038/s41596-020-00489-8.
[51] H. Kim, Y.-T. Kwon, C. Zhu, F. Wu, S. Kwon, W.-H. Yeo, H.J. Choo, Real-time functional assay of volumetric muscle loss injured mouse masseter muscles via nanomembrane electronics, Adv. Sci. 8 (17) (2021) 2101037, https://doi.org/10.1002/advs.v8.1710.1002/advs.202101037.
[52] Z. Lou, S. Chen, L. Wang, K. Jiang, G. Shen, An ultra-sensitive and rapid response speed graphene pressure sensors for electronic skin and health monitoring, Nano Energy. 23 (2016) 7–14, https://doi.org/10.1016/j.nanoen.2016.02.053.
[53] Y. Wang, T. Yang, J. Lao, R. Zhang, Y. Zhang, M. Zhu, X. Li, X. Zang, K. Wang, W. Yu, H.u. Jin, L.i. Wang, H. Zhu, Ultra-sensitive graphene strain sensor for sound signal acquisition and recognition, Nano Res. 8 (5) (2015) 1627–1636, https://doi.org/10.1007/s12274-014-0652-3.
[54] Y. Cheng, R. Wang, J. Sun, L. Gao, A stretchable and highly sensitive graphene-based fiber for sensing tensile strain, bending, and torsion, Adv. Mater. 27 (45) (2015) 7365–7371, https://doi.org/10.1002/adma.201503558.
[55] L.-Q. Tao, H. Tian, Y. Liu, Z.-Y. Ju, Y. Pang, Y.-Q. Chen, D.-Y. Wang, X.-G. Tian, J.-C. Yan, N.-Q. Deng, Y. Yang, T.-L. Ren, An intelligent artificial throat with sound-sensing ability based on laser induced graphene, Nat. Commun. 8 (2017) 14579, https://doi.org/10.1038/ncomms14579.
[56] H. Lee, T.K. Choi, Y.B. Lee, H.R. Cho, R. Ghaffari, L. Wang, H.J. Choi, T.D. Chung, N. Lu, T. Hyeon, S.H. Choi, D.-H. Kim, A graphene-based electrochemical device with thermoresponsive microneedles for diabetes monitoring and therapy, Nat. Nanotechnol. 11 (6) (2016) 566–572, https://doi.org/10.1038/nnano.2016.38.
[57] J. Zhu, S. Liu, Z. Hu, X. Zhang, N. Yi, K. Tang, M.G. Dexheimer, X. Lian, Q. Wang, J. Yang, J. Gray, H. Cheng, Laser-induced graphene non-enzymatic glucose sensors for on-body measurements, Biosens. Bioelectron. 193 (2021) 113606, https://doi.org/10.1016/j.bios.2021.113606.
[58] L. Lipani, B.G.R. Dupont, F. Doungmene, F. Marken, R.M. Tyrrell, R.H. Guy, A. Ilie, Non-invasive, transdermal, path-selective and specific glucose monitoring via a graphene-based platform, Nat. Nanotechnol. 13 (6) (2018) 504–511, https://doi.org/10.1038/s41565-018-0112-4.
[59] Y. Yang, Y.u. Song, X. Bo, J. Min, O.S. Pak, L. Zhu, M. Wang, J. Tu, A. Kogan, H. Zhang, T.K. Hsiai, Z. Li, W. Gao, A laser-engraved wearable sensor for sensitive detection of uric acid and tyrosine in sweat, Nat. Biotechnol. 38 (2) (2020) 217–224, https://doi.org/10.1038/s41587-019-0321-x.
[60] S. Mondal, S.J. Kim, C.-G. Choi, Honeycomb-like MoS2 nanotube array-based wearable sensors for noninvasive detection of human skin moisture, ACS Appl. Mater. Interfaces. 12 (14) (2020) 17029–17038, https://doi.org/10.1021/acsami.9b2291510.1021/acsami.9b22915.s00110.1021/acsami.9b22915.s00210.1021/acsami.9b22915.s003.
[61] Q. Jin, H.-J. Chen, X. Li, X. Huang, Q. Wu, G. He, T. Hang, C. Yang, Z. Jiang, E. Li, A. Zhang, Z. Lin, F. Liu, X.i. Xie, Reduced Graphene Oxide Nanohybrid-Assembled Microneedles as Mini-Invasive Electrodes for Real-Time Transdermal Biosensing, Small. 15 (6) (2019) 1804298, https://doi.org/10.1002/smll.v15.610.1002/smll.201804298.
[62] R.M. Torrente-Rodríguez, J. Tu, Y. Yang, J. Min, M. Wang, Y.u. Song, Y. Yu, C. Xu, C. Ye, W.W. IsHak, W. Gao, Investigation of cortisol dynamics in human sweat using a graphene-based wireless mhealth system, Matter. 2 (4) (2020) 921–937, https://doi.org/10.1016/j.matt.2020.01.021.
[63] L.-Q. Tao, K.-N. Zhang, H.e. Tian, Y. Liu, D.-Y. Wang, Y.-Q. Chen, Y.i. Yang, T.-L. Ren, Graphene-paper pressure sensor for detecting human motions, ACS Nano. 11 (9) (2017) 8790–8795, https://doi.org/10.1021/acsnano.7b0282610.1021/acsnano.7b02826.s001.
[64] X. Chen, F. Luo, M. Yuan, D. Xie, L.i. Shen, K. Zheng, Z. Wang, X. Li, L.-Q. Tao, A dual-functional graphene-based self-alarm health-monitoring e-skin, Adv. Funct. Mater. 29 (51) (2019) 1904706, https://doi.org/10.1002/adfm.v29.5110.1002/adfm.201904706.
[65] J. He, P. Xiao, J. Shi, Y. Liang, W. Lu, Y. Chen, W. Wang, P. Théato, S.-W. Kuo, T. Chen, High performance humidity fluctuation sensor for wearable devices via a bioinspired atomic-precise tunable graphene-polymer heterogeneous sensing junction, Chem. Mater. 30 (13) (2018) 4343–4354, https://doi.org/10.1021/acs.chemmater.8b01587.
[66] Y. Pang, J. Jian, T. Tu, Z. Yang, J. Ling, Y. Li, X. Wang, Y. Qiao, H. Tian, Y. Yang, T.-L. Ren, Wearable humidity sensor based on porous graphene network for respiration monitoring, Biosens. Bioelectron. 116 (2018) 123–129, https://doi.org/10.1016/j.bios.2018.05.038.
[67] H. Guo, C. Lan, Z. Zhou, P. Sun, D. Wei, C. Li, Transparent, flexible, and stretchable WS2 based humidity sensors for electronic skin, Nanoscale. 9 (19) (2017) 6246–6253, https://doi.org/10.1039/C7NR01016H.
[68] A. Gholizadeh, D. Voiry, C. Weisel, A. Gow, R. Laumbach, H. Kipen, M. Chhowalla, M. Javanmard, Toward point-of-care management of chronic respiratory conditions: Electrochemical sensing of nitrite content in exhaled breath condensate using reduced graphene oxide, Microsystems Nanoeng. 3 (2017) 17022, https://doi.org/10.1038/micronano.2017.22.
[69] A. Aasi, S. Mehdi Aghaei, B. Panchapakesan, Outstanding performance of transition-metal-decorated single-layer graphene-like BC6N nanosheets for disease biomarker detection in human breath, ACS, Omega. 6 (7) (2021) 4696–4707, https://doi.org/10.1021/acsomega.0c0549510.1021/acsomega.0c05495.s001.
[70] H. Xu, J.X. Xiang, Y.F. Lu, M.K. Zhang, J.J. Li, B.B. Gao, Y.J. Zhao, Z.Z. Gu, Multifunctional wearable sensing devices based on functionalized graphene films for simultaneous monitoring of physiological signals and volatile organic compound biomarkers, ACS Appl. Mater. Interfaces. 10 (14) (2018) 11785–11793, https://doi.org/10.1021/acsami.8b0007310.1021/acsami.8b00073.s001.
[71] M.S. Mannoor, H. Tao, J.D. Clayton, A. Sengupta, D.L. Kaplan, R.R. Naik, N. Verma, F.G. Omenetto, M.C. McAlpine, Graphene-based wireless bacteria detection on tooth enamel, Nat. Commun. 3 (2012) 763–768, https://doi.org/10.1038/ncomms1767.
[72] B.-U. Hwang, J.-H. Lee, T.Q. Trung, E. Roh, D.-I. Kim, S.-W. Kim, N.-E. Lee, Transparent stretchable self-powered patchable sensor platform with ultrasensitive recognition of human activities, ACS Nano. 9 (9) (2015) 8801–8810, https://doi.org/10.1021/acsnano.5b01835.
[73] Z. Liu, G. Wang, W. Pei, C. Wei, X. Wu, Z. Dou, Y. Li, Y. Wang, H. Chen, Application of graphene nanowalls in an intraocular pressure sensor, J. Mater. Chem. B. 8 (38) (2020) 8794–8802, https://doi.org/10.1039/D0TB01687J.
[74] I.M. Taylor, E.M. Robbins, K.A. Catt, P.A. Cody, C.L. Weaver, X.T. Cui, Enhanced dopamine detection sensitivity by PEDOT/Graphene Oxide coating on in vivo carbon fiber electrodes, Biosens Bioelectron. 89 (2017) 400–410, https://doi.org/10.1016/j.bios.2016.05.084.Enhanced.
[75] T.-C. Liu, M.-C. Chuang, C.-Y. Chu, W.-C. Huang, H.-Y. Lai, C.-T. Wang, W.-L. Chu, S.-Y. Chen, Y.-Y. Chen, Implantable graphene-based neural electrode interfaces for electrophysiology and neurochemistry in in vivo hyperacute stroke model, ACS Appl. Mater. Interfaces. 8 (1) (2016) 187–196, https://doi.org/10.1021/acsami.5b08327.
[76] B.M. Blaschke, N. Tort-Colet, A. Guimerà-Brunet, J. Weinert, L. Rousseau, A. Heimann, S. Drieschner, O. Kempski, R. Villa, M.V. Sanchez-Vives, J.A. Garrido, Mapping brain activity with flexible graphene micro-transistors, 2D Mater. 4 (2) (2017) 025040, https://doi.org/10.1088/2053-1583/aa5eff.
[77] E. Masvidal-Codina, X. Illa, M. Dasilva, A.B. Calia, T. Dragojević, E.E. Vidal-Rosas, E. Prats-Alfonso, J. Martínez-Aguilar, J.M. De la Cruz, R. Garcia-Cortadella, P. Godignon, G. Rius, A. Camassa, E. Del Corro, J. Bousquet, C. Hébert, T. Durduran, R. Villa, M.V. Sanchez-Vives, J.A. Garrido, A. Guimerà-Brunet, High-resolution mapping of infraslow cortical brain activity enabled

by graphene microtransistors, Nat. Mater. 18 (3) (2019) 280–288, https://doi.org/10.1038/s41563-018-0249-4.
[78] X. Chen, Y.J. Park, M. Kang, S.K. Kang, J. Koo, S.M. Shinde, J. Shin, S. Jeon, G. Park, Y. Yan, M.R. MacEwan, W.Z. Ray, K.M. Lee, J.A. Rogers, J.H. Ahn, CVD-grown monolayer MoS2 in bioabsorbable electronics and biosensors, Nat. Commun. 9 (2018) 1690, https://doi.org/10.1038/s41467-018-03956-9.
[79] C.-H. Chen, C.-T. Lin, W.-L. Hsu, Y.-C. Chang, S.-R. Yeh, L.-J. Li, D.-J. Yao, A flexible hydrophilic-modified graphene microprobe for neural and cardiac recording, Nanomedicine Nanotechnology, Biol. Med. 9 (5) (2013) 600–604, https://doi.org/10.1016/j.nano.2012.12.004.
[80] A. Béraud, M. Sauvage, C.M. Bazán, M. Tie, A. Bencherif, D. Bouilly, Graphene field-effect transistors as bioanalytical sensors: Design, operation and performance, Analyst. 146 (2) (2021) 403–428.
[81] W. Fu, L. Jiang, E.P. van Geest, L.M.C. Lima, G.F. Schneider, Sensing at the surface of graphene field-effect transistors, Adv. Mater. 29 (6) (2017) 1603610, https://doi.org/10.1002/adma.201603610.
[82] Y. Yang, N. Huo, J. Li, Sensitized monolayer MoS2 phototransistors with ultrahigh responsivity, J. Mater. Chem. C. 5 (44) (2017) 11614–11619.
[83] Z. Yin, H. Li, H. Li, L. Jiang, Y. Shi, Y. Sun, G. Lu, Q. Zhang, X. Chen, H. Zhang, Single-layer MoS2 phototransistors, ACS Nano. 6 (1) (2012) 74–80, https://doi.org/10.1021/nn2024557.
[84] B.C. Janegitz, T.A. Silva, A. Wong, L. Ribovski, F.C. Vicentini, M.D.P. Taboada Sotomayor, O. Fatibello-Filho, The application of graphene for in vitro and in vivo electrochemical biosensing, Biosens. Bioelectron. 89 (2017) 224–233, https://doi.org/10.1016/j.bios.2016.03.026.
[85] G. Reina, J.M. González-Domínguez, A. Criado, E. Vázquez, A. Bianco, M. Prato, Promises, facts and challenges for graphene in biomedical applications, Chem. Soc. Rev. 46 (15) (2017) 4400–4416.
[86] W. Yan, H.R. Fuh, Y. Lv, K.Q. Chen, T.Y. Tsai, Y.R. Wu, T.H. Shieh, K.M. Hung, J. Li, D. Zhang, C.Ó. Coileáin, S.K. Arora, Z. Wang, Z. Jiang, C.R. Chang, H.C. Wu, Giant gauge factor of Van der Waals material based strain sensors, Nat. Commun. 12 (2021) 2018, https://doi.org/10.1038/s41467-021-22316-8.
[87] M. Zhu, X. Du, S. Liu, J. Li, Z. Wang, T. Ono, A review of strain sensors based on two-dimensional molybdenum disulfide, J. Mater. Chem. C. 9 (29) (2021) 9083–9101, https://doi.org/10.1039/D1TC02102H.
[88] A.M. Pinto, I.C. Gonçalves, F.D. Magalhães, Graphene-based materials biocompatibility: A review, Colloids Surfaces B Biointerfaces. 111 (2013) 188–202, https://doi.org/10.1016/j.colsurfb.2013.05.022.
[89] B. Fadeel, C. Bussy, S. Merino, E. Vázquez, E. Flahaut, F. Mouchet, L. Evariste, L. Gauthier, A.J. Koivisto, U. Vogel, C. Martín, L.G. Delogu, T. Buerki-Thurnherr, P. Wick, D. Beloin-Saint-Pierre, R. Hischier, M. Pelin, F. Candotto Carniel, M. Tretiach, F. Cesca, F. Benfenati, D. Scaini, L. Ballerini, K. Kostarelos, M. Prato, A. Bianco, Safety assessment of graphene-based materials: focus on human health and the environment, ACS Nano. 12 (11) (2018) 10582–10620, https://doi.org/10.1021/acsnano.8b0475810.1021/acsnano.8b04758.s001.
[90] C.J. Bullock, C. Bussy, Biocompatibility considerations in the design of graphene biomedical materials, Adv. Mater. Interfaces. 6 (2019) 1900229, https://doi.org/10.1002/admi.201900229.
[91] D. Nguyen, M. Valet, J. Dégardin, L. Boucherit, X. Illa, J. de la Cruz, E. del Corro, J. Bousquet, J.A. Garrido, C. Hébert, S. Picaud, Novel graphene electrode for retinal implants: an in vivo biocompatibility study, Front. Neurosci. 15 (2021), https://doi.org/10.3389/fnins.2021.615256 615256.
[92] A. Bourrier, P. Shkorbatova, M. Bonizzato, E. Rey, Q. Barraud, G. Courtine, R. Othmen, V. Reita, V. Bouchiat, C. Delacour, Monolayer graphene coating of intracortical probes for long-lasting neural activity monitoring, Adv. Healthc. Mater. 8 (18) (2019) 1801331, https://doi.org/10.1002/adhm.v8.1810.1002/adhm.201801331.
[93] N.V. Apollo, M.I. Maturana, W. Tong, D.A.X. Nayagam, M.N. Shivdasani, J. Foroughi, G.G. Wallace, S. Prawer, M.R. Ibbotson, D.J. Garrett, Soft, flexible freestanding neural stimulation and recording electrodes fabricated from reduced graphene oxide, Adv. Funct. Mater. 25 (23) (2015) 3551–3559, https://doi.org/10.1002/adfm.201500110.
[94] D. Kireev, Graphene & two-dimensional devices for bioelectronics and neuroprosthetics, 2D Mater. 5 (2018), https://doi.org/10.1088/2053-1583/aad988, 042004.
[95] M. Frost, M.E. Meyerhoff, In vivo chemical sensors: Tackling biocompatibility, Anal. Chem. 78 (21) (2006) 7370–7377, https://doi.org/10.1021/ac069475k.
[96] C.C. Dos Santos, G.N. Lucena, G.C. Pinto, M.J. Júnior, R.F.C. Marques, Advances and current challenges in non-invasive wearable sensors and wearable biosensors—A mini-review, Med. Devices Sensors. 4 (2021), https://doi.org/10.1002/mds3.10130 e10130.
[97] D. Ding, Y. Lu, R. Zhao, X. Liu, C. De-Eknamkul, C. Ren, A. Mehrsa, T. Komiyama, D. Kuzum, Evaluation of Durability of Transparent Graphene Electrodes Fabricated on Different Flexible Substrates for Chronic in Vivo Experimentsof durability of transparent graphene electrodes fabricated on different flexible substrates for chronic in vivo experim, IEEE Trans. Biomed. Eng. 67 (11) (2020) 3203–3210, https://doi.org/10.1109/TBME.2020.2979475.
[98] J. Kim, Y. Lee, M. Kang, L. Hu, S. Zhao, J.-H. Ahn, 2D materials for skin-mountable electronic devices, Adv. Mater. 33 (47) (2021) 2005858, https://doi.org/10.1002/adma.v33.4710.1002/adma.202005858.
[99] H. Huang, S. Su, N. Wu, H. Wan, S. Wan, H. Bi, L. Sun, Graphene-based sensors for human health monitoring, Front. Chem. 7 (2019) 399, https://doi.org/10.3389/fchem.2019.00399.
[100] Z. Pu, J. Tu, R. Han, X. Zhang, J. Wu, C. Fang, H. Wu, X. Zhang, H. Yu, D. Li, A flexible enzyme-electrode sensor with cylindrical working electrode modified with a 3D nanostructure for implantable continuous glucose monitoring, Lab Chip. 18 (23) (2018) 3570–3577, https://doi.org/10.1039/C8LC00908B.
[101] H. Wu, G. Yang, K. Zhu, S. Liu, W. Guo, Z. Jiang, Z. Li, Materials, devices, and systems of on-skin electrodes for electrophysiological monitoring and human–machine interfaces, Adv. Sci. 8 (2) (2021) 2001938, https://doi.org/10.1002/advs.v8.210.1002/advs.202001938.
[102] Y. Liu, M. Pharr, G.A. Salvatore, Lab-on-Skin: a review of flexible and stretchable electronics for wearable health monitoring, ACS Nano. 11 (10) (2017) 9614–9635, https://doi.org/10.1021/acsnano.7b04898.
[103] Y. Zhou, D. Dai, Y.u. Gao, Z. Zhang, N. Sun, H. Tan, X. Cai, J. Cai, Recent advances in graphene electronic skin and its future prospects, ChemNanoMat. 7 (9) (2021) 982–997, https://doi.org/10.1002/cnma.202100198.
[104] M. Amjadi, K.-U. Kyung, I. Park, M. Sitti, Stretchable, skin-mountable, and wearable strain sensors and their potential applications: a review, Adv. Funct. Mater. 26 (11) (2016) 1678–1698, https://doi.org/10.1002/adfm.201504755.
[105] M. Pelin, L. Fusco, V. León, C. Martín, A. Criado, S. Sosa, E. Vázquez, A. Tubaro, M. Prato, Differential cytotoxic effects of graphene and graphene oxide on skin keratinocytes, Sci. Rep. 7 (2017) 40572, https://doi.org/10.1038/srep40572.
[106] M. Pelin, S. Sosa, M. Prato, A. Tubaro, Occupational exposure to graphene based nanomaterials: Risk assessment, Nanoscale. 10 (34) (2018) 15894–15903.
[107] K.-H. Liao, Y.-S. Lin, C.W. Macosko, C.L. Haynes, Cytotoxicity of graphene oxide and graphene in human erythrocytes and skin fibroblasts, ACS Appl. Mater. Interfaces. 3 (7) (2011) 2607–2615, https://doi.org/10.1021/am200428v.
[108] L. Fusco, M. Garrido, C. Martín, S. Sosa, C. Ponti, A. Centeno, B. Alonso, A. Zurutuza, E. Vázquez, A. Tubaro, M. Prato, M. Pelin, Skin irritation potential of graphene-based materials using a non-animal test, Nanoscale. 12 (2) (2020) 610–622.
[109] W. Chen, W. Qi, W. Lu, N.R. Chaudhury, J. Yuan, L. Qin, J. Lou, Direct assessment of the toxicity of molybdenum disulfide atomically thin film and microparticles via cytotoxicity and patch testing, Small. 14 (12) (2018) 1702600, https://doi.org/10.1002/smll.v14.1210.1002/smll.201702600.
[110] M.A. Shathi, M. Chen, N.A. Khoso, M.T. Rahman, B. Bhattacharjee, Graphene coated textile based highly flexible and washable sports bra for human health monitoring, Mater. Des. 193 (2020) 108792, https://doi.org/10.1016/j.matdes.2020.108792.
[111] Y. Wei, X. Li, Y. Wang, T. Hirtz, Z. Guo, Y. Qiao, T. Cui, H.e. Tian, Y.i. Yang, T.-L. Ren, Graphene-Based Multifunctional Textile for Sensing and Actuating, Graphene-based multifunctional textile for sensing and actuating 15 (11) (2021) 17738–17747, https://doi.org/10.1021/acsnano.1c05701.
[112] D. Du, P. Li, J. Ouyang, Graphene coated nonwoven fabrics as wearable sensors, J. Mater. Chem. C. 4 (15) (2016) 3224–3230, https://doi.org/10.1039/C6TC00350H.
[113] E. Messas, M. Pernot, M. Couade, Arterial wall elasticity: State of the art and future prospects, Diagn. Interv Imaging. 94 (5) (2013) 561–569, https://doi.org/10.1016/j.diii.2013.01.025.
[114] M. Etemadi, O.T. Inan, Wearable ballistocardiogram and seismocardiogram systems for health and performance, J. Appl. Physiol. 124 (2) (2018) 452–461, https://doi.org/10.1152/japplphysiol.00298.2017.
[115] Q. Liu, J.i. Chen, Y. Li, G. Shi, High-performance strain sensors with fish-scale-like graphene-sensing layers for full-range detection of human motions, ACS Nano. 10 (8) (2016) 7901–7906, https://doi.org/10.1021/acsnano.6b0381310.1021/acsnano.6b03813.s001.
[116] Z. Wang, J. Shin, J.-H. Park, H. Lee, D.-H. Kim, H. Liu, Engineering materials for electrochemical sweat sensing, Adv. Funct. Mater. 31 (12) (2021) 2008130, https://doi.org/10.1002/adfm.v31.12.
[117] G. Li, D. Wen, Sensing nanomaterials of wearable glucose sensors, Chinese Chem. Lett. 32 (1) (2021) 221–228, https://doi.org/10.1016/j.cclet.2020.10.028.
[118] S. Borini, R. White, D. Wei, M. Astley, S. Haque, E. Spigone, N. Harris, J. Kivioja, T. Ryhänen, Ultrafast graphene oxide humidity sensors, ACS Nano. 7 (12) (2013) 11166–11173, https://doi.org/10.1021/nn404889b.
[119] A. Hermawan, T. Amrillah, A. Riapanitra, W.-J. Ong, S. Yin, Prospects and challenges of MXenes as emerging sensing materials for flexible and wearable breath-based biomarker diagnosis, Adv. Healthc. Mater. 10 (20) (2021) 2100970, https://doi.org/10.1002/adhm.v10.20.
[120] R. Goldoni, M. Farronato, S.T. Connelly, G.M. Tartaglia, W.-H. Yeo, Recent advances in graphene-based nanobiosensors for salivary biomarker detection, Biosens. Bioelectron. 171 (2021) 112723, https://doi.org/10.1016/j.bios.2020.112723.
[121] H. Tian, X. Wang, F. Wu, Y. Yang, T.-L. Ren, High performance 2D perovskite/graphene optical synapses as artificial eyes, in: 2018 IEEE Int. Electron Devices Meet., 2018: pp. 38.6.1-38.6.4. https://doi.org/10.1109/IEDM.2018.8614666.
[122] S. Li, Y. Zhang, W. Yang, H. Liu, X. Fang, 2D Perovskite Sr2Nb3O10 for high-performance UV photodetectors, Adv. Mater. 32 (7) (2020) 1905443, https://doi.org/10.1002/adma.v32.7.
[123] W. Song, J. Chen, Z. Li, X. Fang, Self-Powered MXene/GaN van der Waals heterojunction ultraviolet photodiodes with superhigh efficiency and stable current outputs, Adv. Mater. 33 (27) (2021) 2101059, https://doi.org/10.1002/adma.v33.27.
[124] S. Cai, X. Xu, W. Yang, J. Chen, X. Fang, Materials and designs for wearable photodetectors, Adv. Mater. 31 (18) (2019) 1808138, https://doi.org/10.1002/adma.v31.18.

[125] H. Sun, W. Tian, F. Cao, J. Xiong, L. Li, Ultrahigh-Performance Self-Powered Flexible Double-Twisted Fibrous broadband perovskite photodetector, Adv. Mater. 30 (21) (2018) 1706986, https://doi.org/10.1002/adma.v30.21.
[126] K. Kostarelos, M. Vincent, C. Hebert, J.A. Garrido, Graphene in the design and engineering of next-generation neural interfaces, Adv. Mater. 29 (42) (2017) 1700909, https://doi.org/10.1002/adma.201700909.
[127] Y. Lu, H. Lyu, A.G. Richardson, T.H. Lucas, D. Kuzum, Flexible neural electrode array based-on porous graphene for cortical microstimulation and sensing, Sci. Rep. 6 (2016) 33526, https://doi.org/10.1038/srep33526.
[128] J. Lin, R. Fu, X. Zhong, P. Yu, G. Tan, W. Li, H. Zhang, Y. Li, L. Zhou, C. Ning, Wearable sensors and devices for real-time cardiovascular disease monitoring, Cell Reports Phys. Sci. 2 (8) (2021) 100541, https://doi.org/10.1016/j.xcrp.2021.100541.
[129] K.N. Alagarsamy, S. Mathan, W. Yan, A. Rafieerad, S. Sekaran, H. Manego, S. Dhingra, Carbon nanomaterials for cardiovascular theranostics: Promises and challenges, Bioact. Mater. 6 (8) (2021) 2261–2280, https://doi.org/10.1016/j.bioactmat.2020.12.030.
[130] K. Veerubhotla, C.H. Lee, Emerging trends in nanocarbon-based cardiovascular applications, Adv. Ther. 3 (7) (2020) 1900208, https://doi.org/10.1002/adtp.v3.7.
[131] M.M. Hasan, M.M. Hossain, Nanomaterials-patterned flexible electrodes for wearable health monitoring: a review, J. Mater. Sci. 56 (27) (2021) 14900–14942, https://doi.org/10.1007/s10853-021-06248-8.
[132] M.C. Frost, M.E. Meyerhoff, Real-time monitoring of critical care analytes in the bloodstream with chemical sensors: progress and challenges, Annu. Rev. Anal. Chem. 8 (1) (2015) 171–192, https://doi.org/10.1146/annurev-anchem-071114-040443.
[133] Y. Chai, X. Ma, X. Zang, X. Wang, N. Zhu, Z. Xie, J. Ji, X. Zhang, M. Xue, Cold direct pen writing of reduced graphene oxide foams for ultrasensitive micro-contact force probing, Carbon N. Y. 157 (2020) 140–146, https://doi.org/10.1016/j.carbon.2019.10.031.
[134] Y. Qiao, X. Li, T. Hirtz, G.e. Deng, Y. Wei, M. Li, S. Ji, Q.i. Wu, J. Jian, F. Wu, Y. Shen, H.e. Tian, Y.i. Yang, T.-L. Ren, Graphene-based wearable sensors, Nanoscale. 11 (41) (2019) 18923–18945, https://doi.org/10.1039/C9NR05532K.
[135] W. Gao, S. Emaminejad, H.Y.Y. Nyein, S. Challa, K. Chen, A. Peck, H.M. Fahad, H. Ota, H. Shiraki, D. Kiriya, D.-H. Lien, G.A. Brooks, R.W. Davis, A. Javey, Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis, Nature. 529 (7587) (2016) 509–514, https://doi.org/10.1038/nature16521.