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Flexible bioelectronics for physiological signals sensing and disease treatment

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A B S T R A C T

Flexible bioelectronics, including wearable and implantable electronics, have revolutionized the way of human-machine interaction due to the fact that they can provide natural and seamless interactions with humans and keep stable and durable at strained states. As sensor elements or biomimetic actuators, flexible bioelectronics can dynamically sense and monitor physiological signals, reveal real-time physical health information and provide timely precise stimulations or treatments. Thus, the flexible bioelectronics are playing increasingly important roles in human-health monitoring and disease treatment, which will significantly change the future of healthcare as well as our relationships with electronics. This review summarizes recent major progress in the development of flexible substrates or encapsulation materials, sensors, circuits and energy-autonomous powers toward digital healthcare monitoring, emphasizing its role in biomedical applications in vivo and problems in practical applications. A future perspective into the challenges and opportunities in emerging flexible bioelectronics designs for the next-generation healthcare monitoring systems is also presented.

Contents

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1. Introduction

With rapid development of functional materials and manufacturing techniques, flexible bioelectronics have evolved into playing important roles in clinic and daily life from in vitro to in vivo [1–3]. Although conventional healthcare workflow as the conventional clinical applications can detect the physiological signals and reveal health information, they can only offer snapshots of the physiological condition of the body and involve large-sized extracorporeal devices or require patient hospitalization [4]. In comparison, rapid development in science and technology has drastically reduced or even eliminated the spatial separation between human and flexible bioelectronics to render comfortable wearability or implantability [5,6]. In particular, a significant interest of flexible bioelectronics lies in monitoring physiological signals in real-time, revealing timely information on the state of our body and further providing actionable feedback for disease treatment to sustain a healthy lifestyle [7,8].

In recent years, commercial wearable bioelectronics are incorporated into clothing and smartwatches, rendering them the ability to monitor body temperature, measure pulse rate, and even analyze heart waveforms [9]. However, the parameters that can be measured with such systems are narrow in scope and have low levels of clinical relevance/accuracy due to the sensing components loosely coupled to the human bodies. Thus, the inability to form stable, intimate tissue interfaces with these rigid wearable system remains a fundamental constraint in their measurement capabilities. To overcome these limitations, flexible bioelectronics explored strategies in both material science and deterministic architectures to achieve a low modulus close to our skin or the surfaces of internal organs to transduce physiological signals [10,11]. Good adhesion, absolute extensibility and mechanical imperceptibility are important features of flexible bioelectronics. Beyond designing conformal bioelectronics, ascribing functionalities in these bioelectronics are of utmost importance for high selectivity and sensitivity to further develop a precise, dynamical and real-time healthcare system.

Flexible bioelectronics, human body and mobile electronic devices make up a physiological signal monitoring, timely treatment and health information cloud storage system [12–14]. The design of the flexible electronics and working principle of the biomedical system was shown in Fig. 1. The general structure of flexible bioelectronics is composed of a flexible substrate or encapsulation layer, multifunctional sensors to obtain various signals, integrated circuits to electrically process the signals and a power supply (Fig. 1a). As shown in Fig. 1b, human bodies consist of a number of biological systems (organs and tissues) that carry out specific functions necessary for everyday living, and the physiological signals can be captured and monitored by flexible bioelectronics during natural physiological processes from the human body. In addition, as shown in Fig. 1c, the wireless transmission can be designed to convey the analyzed data and feedback to the user for smart health care. Based on monitoring and assessment of physical condition, in reverse, flexible bioelectronics can also act as actuators to provide timely precise stimulation or treatment [15–17].

This paper highlights the latest advances in this emerging field of flexible bioelectronics, with particular emphasis on device design strategies and pioneering conceptual bio-applications that have the potential to shape the directions of future developments. This review begins with an introductory section of strategies to structural design principles and several concepts of flexible bioelectronics, including flexible substrate or encapsulation materials, integrated circuits and power sources. The second part highlights the physiological signals sensing of flexible bioelectronics, classified based on different physiological signal types (biophysical and biochemical signals). In addition, we summarize the biomedical applications of flexible bioelectronics as actuators for diseases treatment in vivo, classified according to their working modes (pharmacological or non-pharmacological therapy). Finally, the review concludes with an overview of key remaining challenges and a summary of opportunities where flexible bioelectronics will be critically important in daily life and in clinic.

2. Flexible bioelectronics composition

The general structure of flexible bioelectronics is composed of various functional devices, including flexible substrates or encapsulation layers, multifunctional sensors to obtain various physiological signals from human body, circuits to electrically process the signals and a power supply [15,16,18]. As the most important component, working mechanisms for biosensors with different sensing targets are discussed in detail in Section 3.

2.1. Substrates or encapsulation materials

A flexible supporting substrate or an encapsulation layer is to ensure the flexible conformal contact between human bodies and electronics. Stretchability is a basic requirement for the bioelectronics to conformably cover the non-developable surface of human body or organs [16,19]. In addition, it will improve the overall robustness to avoid mechanical failure incurred during various human motions. From the material standpoint, the wide availability of polymeric materials provides freedom of choice to cater to the requirements [19]. At the molecular level, for a system to endow mechanical flexibility and stretchability, design strategies leverage on engineering methodologies to modify the molecular structure and its arrangements (Fig. 2a) [20–22]. There are two main concepts to develop electronic materials with intrinsic stretchabilities: one approach is to tailor the molecular structure of the polymeric to ameliorate the rigidity of the polymeric backbone, and the other approach relies on reducing van der Waals forces [20,21]. Many silicone elastomers, such as polydimethylsiloxane

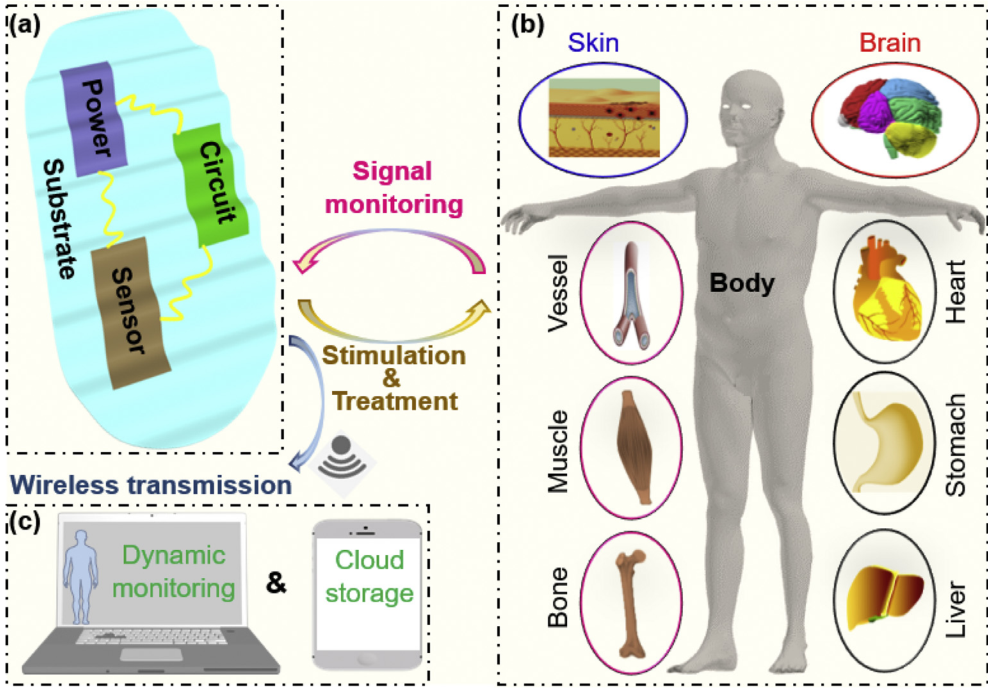

Fig. 1. Design and working principle of the flexible bioelectronics. **(a)** Schematic illustration of structure of flexible bioelectronics composed of functional devices: substrate, sensor, circuit, and power supply. **(b)** Physiological signals monitoring. **(c)** Wireless transmission.

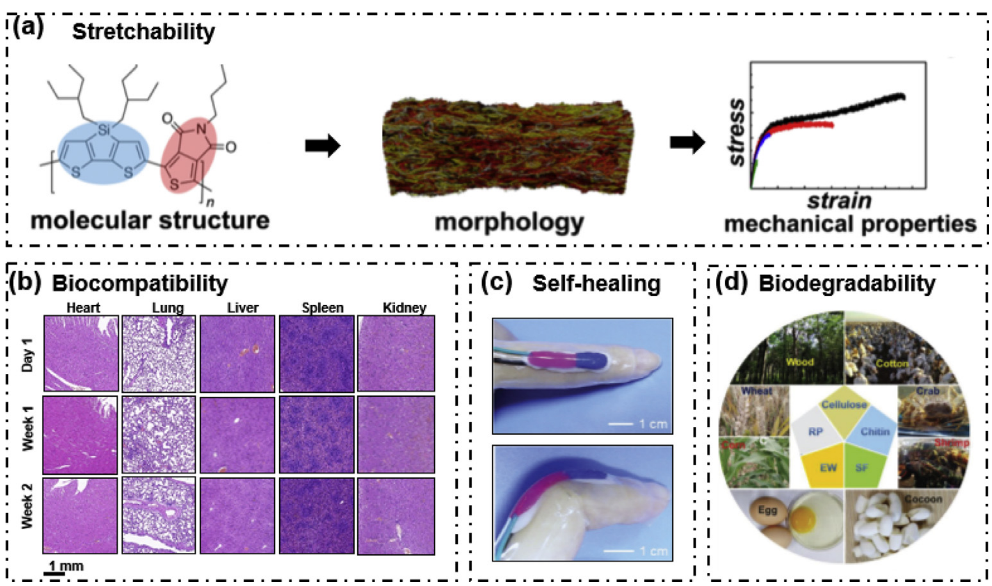

Fig. 2. Substrates or encapsulation materials for flexible electronics. **(a)** Engineering methodologies for intrinsic stretchability [22]. **(b)** Biocompatibility of substrate material [29]. **(c)** Self-healing material [35]. **(d)** Biodegradable materials for biomedical applications [32].

(PDMS) and Ecoflex, have been used extensively as proof of concepts for wearable substrates due to their stretchability and ease of fabrication. In addition, other forms of substrate exist to fulfill different requirements. For example, textile and paper-based substrates represent a specialized class of flexible and stretchable material substrates that transcends beyond molecular engineering [23,24]. On the base of ensuring the flexibility and stretchability of the substrate, biocompatibility is another basic requirement since substrate or encapsulation materials in direct contact with the body is of critical importance for ensuring not only an irritation free interface but also eliminating risks of allergic or toxic reactions [25–27]. Various biocompatible materials have been developed for biomedical applications, such as common insulating medical-grade silicones [28–30], which have the property of non-cytotoxic to ensure that human or animals are in a good health condition during wearing or implanting the flexible bioelectronics (Fig. 2b).

In recent years, developments in new classes of materials also present novel desired features such as self-healing capability and biodegradability [15,31–34]. Self-healing materials, which are able to plastically deform to fully match curved and dynamic surfaces, restore their original shape/condition and further eliminate the necessity of replenishing after damage (Fig. 2c) [35,36]. This

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material shows great potential in applications such as artificial intelligence and personal healthcare. Biodegradable electronic materials capable of breaking down into harmless components in body fluid can drastically reduce pollution from electronic waste [33,34]. The biodegradable materials evolved from synthetic polymers to natural polymers, which can be broadly categorized into organic materials (especially polymers) and inorganic materials. For example, cellulose, silk fibroin, and shellac are biodegradable polymers which are present in nature (Fig. 2d) [32]. In addition, synthetic biodegradable polymers (PVA, polylactic acid, polycaprolactone, polyurethane, polyethylene glycol, polylactic-co-glycolic acid) have been utilized for biomedical applications [16,37]. Flexible bioelectronics based on these biodegradable materials can be break down in body fluid to enable nonsurgical removal after they have completed tissue repair.

2.2. Flexible circuits

To render the flexibility and stretchability of the bioelectronics supported or encapsulated by flexible substrates, circuit engineering is another important factor to keep inorganic electronics stable and durable at strained states [15,16,38]. As the important interconnection components of bioelectronics, flexible circuits play an important role in electrical transmissions between the functional components and human-machine interfaces [39]. To this end, there are several strategies to design the flexible property of the circuits, including liquid metals, material modification and circuit geometry architecture design.

2.2.1. Liquid metals and material modification

Liquid metals are compelling materials for soft and stretchable electrodes as they are metallic conductors with intrinsic infinite deformability. As a substitute to solid-state materials, conductive liquids may be included into elastic substrates as microfluidic interconnects [40–42]. The amorphous liquid state of such materials at room temperature, typically owing to low melting points and high boiling points. Liquid metals can be injected into an enclosed elastomeric substrate with micro channels, which can provide mobility and maintain conductivity of liquid metals under large or 3D deformations. Liquid-phase eutectic gallium indium (EGaIn), different from mercury, offer great promise for flexible bioelectronics due to low toxicity, high conductivity and good electrical stability [43–45]. As an example, Majidi group reported soft and highly deformable circuit interconnects that are electromechanically stable under strained state (Fig. 3a) [46]. The circuit is composed of EGaIn droplets embedded in a soft insulating silicone elastomer, and the droplets rupture to form new connections with neighbours when damaged to form locally conductive pathways with high electrical conductivity, which can act as electrically self-healing circuit interconnects under extreme mechanical damage. However, circuit damage and leakage of the liquid metal is a huge hidden danger to human health [47].

To avoid the toxicity of liquid metals, biocompatible metallic-based components can form the electrical interconnects owing to their inertness and high electrical conductivity [15,48]. The challenge is to convert these rigid metallic elements to be flexible and even stretchable. In this regard, these metallic materials can be deposited or printed on the stretchable substrates as flexible interconnects using micro/nanofabrication methods. Importantly, by reducing the lateral and vertical scale of the materials, the load-bearing stress will be transferred to the base substrate. By altering the chemical processes, materials of different conformations may be built from 0D nanoparticles, 1D nanowires (NWs), to 2D nanosheets/nanomesh [19,49]. Intuitively, different shapes of nanomaterials define the percolation network and junction-contacts, resulting in varying degrees of mechanical robustness and electrical stability. Thus, many researchers have sought different shapes and sizes of nanomaterials to achieve better performance. NWs have been particularly demonstrated and well utilized in many flexible electronics applications, owing to its efficiency for carrier flows [15,19]. For example, Ag and Cu NWs have been acknowledged as ideal candidates for stretchable interconnects. The NW provides strength and size dependent elastic property compared to bulk Ag or Cu, and the deformable NW percolation network also contributes to minimal conductivity change under strain. Graphene/Ag NWs hybrid structures as high performance, transparent, and stretchable electrodes were reported by Lee and co-workers (Fig. 3b) [50]. The percolating networks of metal-NWs with high densities above the percolation threshold were integrated into graphene, which ensure low resistance (~33 Ω/sq), high transmittance (94%), robust conductivity stability and good mechanical flexibility and stretchability (maximum stretching strain of 100%). This hybrid was utilized to build soft eye contact lenses as an example of wearable application. However, the circuit based on material modification usually involves complex processes and functions within a limited range of strain [49,51]. Thus, researchers are constantly exploring other circuit flexibility methods.

2.2.2. Geometry architecture design

Instead of modifying the materials themselves to achieve flexibility and stretchability, using geometry architecture design to realize flexible circuits by traditional inorganic materials is also a hot research field. Utilizing wavy structure can obtain promising stretchablilty to avoid material fractures while maintaining high conductivity performance under strain, due to the fact that wavy structures accommodate compressive and tensile strains through changes in the wave amplitudes and wavelengths rather than through potentially destructive strains in the materials themselves [39,58]. The strain induced into the conductive materials during the stretching/relaxing cycles is the main limiting factor for the longevity and overall performance of the stretchable conductor. Rogers group fabricated periodic wave-structure silicon nanomembranes on silicon elastic substrates and systematically studied the mechanical properties [59–61]. Recently, Chen group reported a high stretchable and conductive Au electrode with wavy structure for neural signal recording (Fig. 3c) [52]. The results indicated that the electrodes have high stretchability and excellent stability (10000 cycles), which is benefit for long-term monitoring. Although the wavy structure made a breakthrough in geometric design for circuit flexibility, it only works stably within a limited small strain range.

Serpentine is another novel approach enhance the flexibility and stretchability of interconnects within a large strain range, which exploits deterministic architecture to accommodate strain [53,62,63]. Rogers group recently reported epidermal electronic systems based on serpentine structures (Fig. 3d, left) [53], which provide a conformal contact with human skin via the action of van der Waals forces and keep reversible and elastic responses against large deformations. The serpentine structure has ultralow effective moduli, bending stiffness, and area densities. Particularly, contact conformity can be promoted with serpentine structure width decreasing, which is attributed to high mechanical robustness and high performance in the process of signal recording. Thus, the serpentine interconnect circuits were applied in a lot of multi-functional epidermal devices to ensure stable electrical conduction. For example, the stretchability of the stretchable lithium ion battery system is more than 4 times larger than previous reports, enabling high areal coverages (50%) of active materials (cathode and anode) at the same time (Fig. 3d, right) [54]. It is believed that

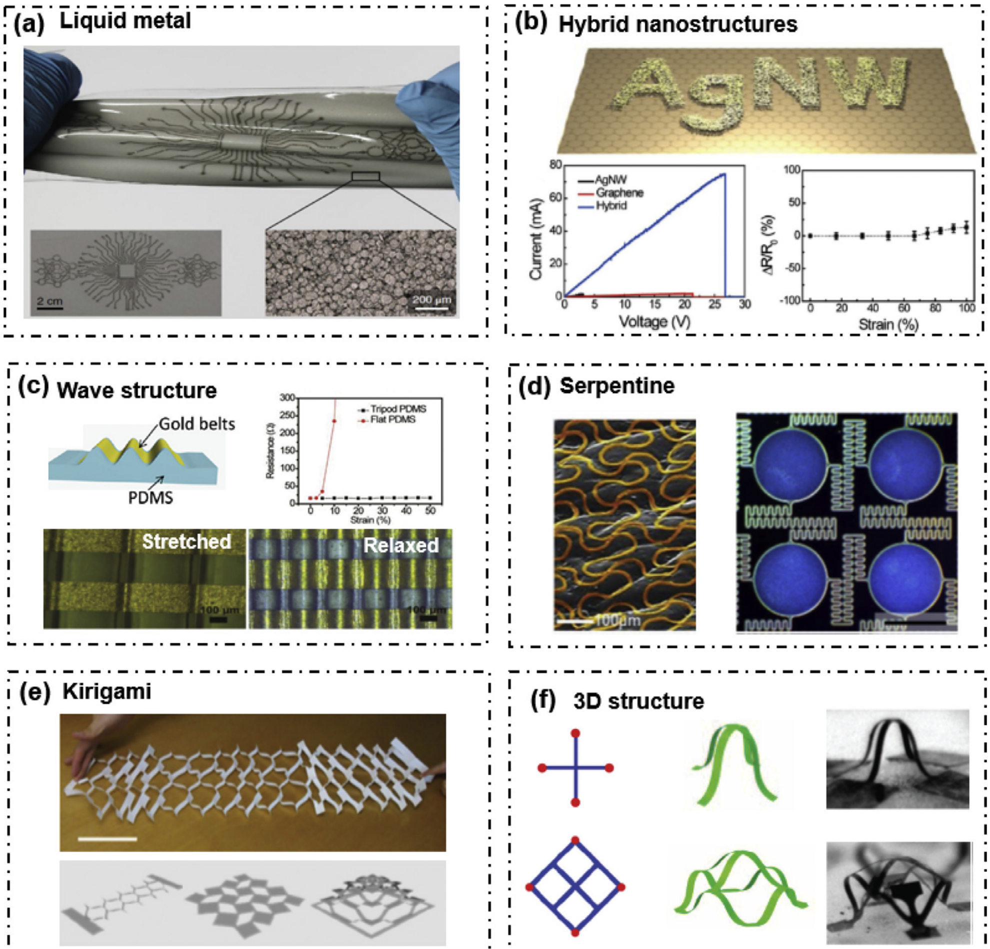

Fig. 3. Design strategies of circuit for flexible bioelectronics. (a) Circuit of liquid metals [46]. **(b)** Graphene/Ag NWs hybrid structures [50]. **(c)** Conductive Au electrode with wave structure [52]. **(d)** Stretchable serpentine electrodes [53,54]. **(e)** Stretchable kirigami electrodes [55,56]. **(f)** 3D architectures through compressive buckling [57].

the serpentine structure will play a key role in flexible bioelectronics.

With high tensile strain (>50%), to achieve stretchability without degradation of electrical and mechanical properties is very challenging even with extraordinary properties of nanocomposites and stretchable serpentine structure. Kirigami, known as the art of paper cutting, is a novel design strategy to render stretchable electronics, including skin-like electronics, implantable biodegradable devices and bio-inspired soft robotics, which offers a universal strategy for engineering stretchable electrodes regardless of materials [64,65]. Ren group reported a highly stretchable and transparent Au nanomesh electrodes on elastomers with kirigami patterns [55]. Through macroscopic laser-cut paper and microscopic observations of nanomeshes (Fig. 3e, top), they concluded that larger ratio of mesh-size to wire-width leads to better stretchability. In addition, Won and co-workers developed a transparent and stretchable kirigami electrodes consisting of ultrathin and flexible AgNWs/cPI composites (Fig. 3e, bottom) [56]. Diverse shapes of stretchable electronics with multivariable configurability can attribute to tailor-designing the stretchability range for anywhere on the body. These kirigami engineered patterns have an ultrastretchability (0 to over 400%), excellent strain reversibility (>10000 cycles). The stretchability range of the circuit with kirigami structure can be tailored depending on the skin-modulus, body parts, human size, and other application requirements.

Another approach to achieve constant conductivity of interconnects is to utilize 3D architectures, which are free from material fracture and self-contact [66–68]. Xu and co-workers developed a strategy to assemble materials into 3D architectures through compressive buckling (Fig. 3f) [57]. To fabricate 3D architectures, the flexible substrates are initially pre-stretched, followed by releasing after the conductive material deposition. More than 40 representative geometries were successfully assembled and studied systematically from the aspects of experiment and mechanical simulation. Although great advancements have been achieved in developments of 3D architectures, the development of 3D-architecture circuits remains in its infancy.

2.3. Power source

Flexible and stable power source is essential for allowing the tissue-mountable bioelectronics to function reliably and continuously in bio-integrated platforms, which are demanding requirements and great challenges for power design strategies [16,19].

2.3.1. Battery

To meet requirements of bio-interfaced applications, commercial rechargeable batteries are the most obvious choice because they were first applied in portable electronic devices [18,75,76]. Rogers group recently developed a rechargeable lithium ion battery technology fabricated on elastomer and connected by serpentine interconnects (Fig. 4a) [54], enabling high reversible stretchability (300%), high capacity densities (~1.1 mAhcm^{-2}) and little loss in capacity for recharging (20 cycles). The good performance can be attributed to the segmented layouts and deformable electrical interconnects, which provides a binding site for the conventional power sources and flexible bioelectronics. However, this device faces the trouble of multiple periodic charging, despite the wireless charging function.

2.3.2. Solar cell

Flexible solar cells (photovoltaic cell) can be adhered conformally to tissues and skin, and they can offer another potentially promising strategy for battery-free power sources in flexible bioelectronics due to mechanical and thermal stability [77–79]. Park and co-workers developed self-powered ultra-flexible electronic devices that can measure biometric signals with very high signal-to-noise ratios when applied to skin or other tissue (Fig. 4b) [69]. The device showed high power-conversion efficiency (10.5%) and

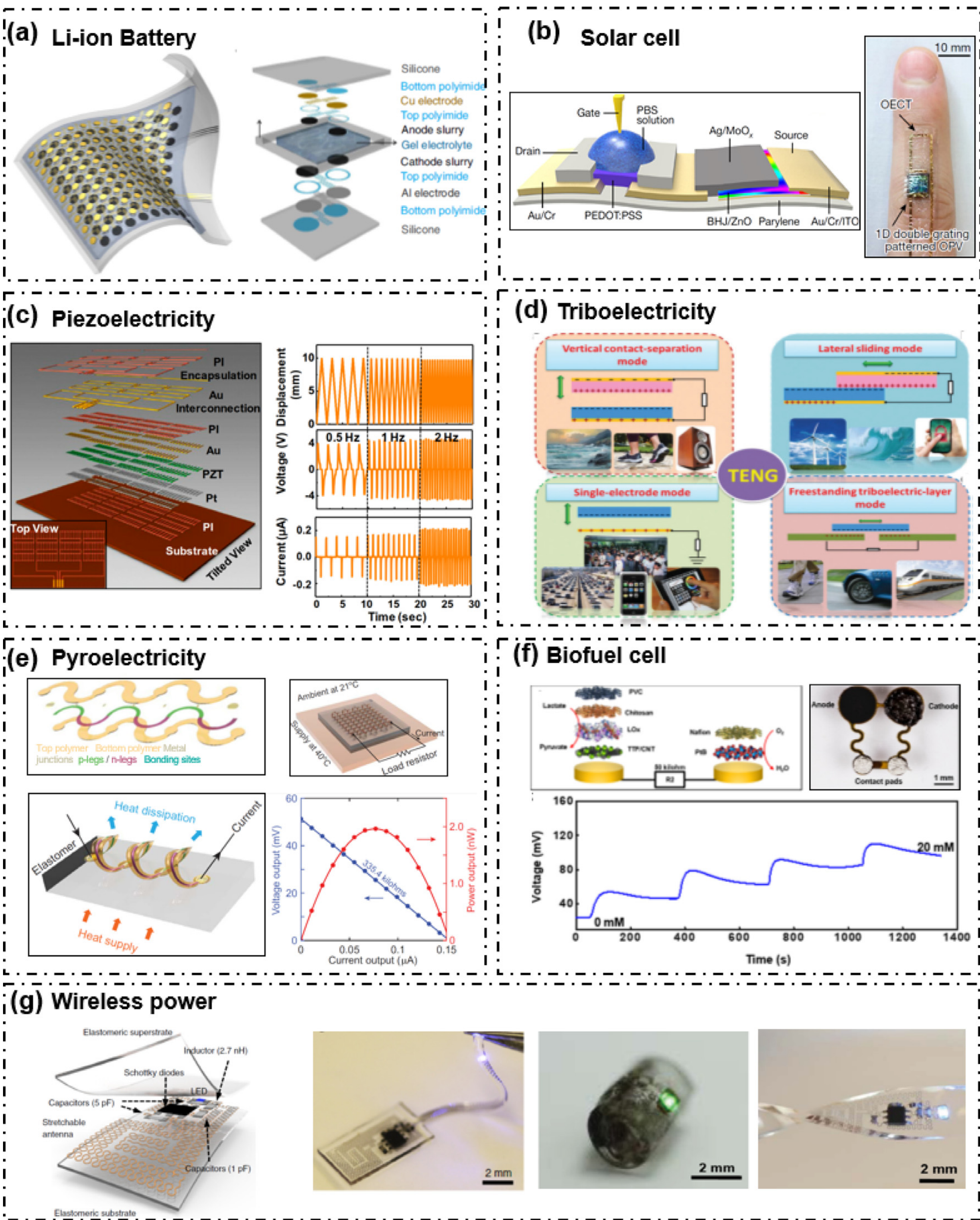

Fig. 4. Flexible, lightweight and stable power sources. (a) Stretchable rechargeable lithium ion battery [54]. **(b)** A flexible solar cells [69]. **(c)** Flexible piezoelectric PZT ribbons [70]. **(d)** Triboelectric generators [71]. **(e)** 3D compliant and stretchable thermoelectric coils [72]. **(f)** Biofuel cells for sweat sensors [73]. **(g)** A wireless power [74].

high power-per-weight (11.46/g), which has been successfully used for cardiac signal detection with a maximum signal-to-noise ratio (40.02). This work provides a new way to dynamically monitor physiological signals using the solar cell as the power source.

2.3.3. Piezoelectricity

As another batteryless power source, flexible piezoelectric devices can also generate sufficient power from human mechanical motion to continuously drive small epidermal biosensor with low power consumption [70,80,81]. The performance of inorganic piezoelectric materials is better than that of organic materials, however, it is very difficult to apply inorganic materials into actual devices due to their rigid and brittle properties. Rogers group developed flexible mechanical energy harvester based on piezoelectric PZT ribbons, enabling high efficiency mechanical-to-electrical energy conversion from the natural contractile and relaxation motions of the heart, lung, and diaphragm (Fig. 4c) [33]. The biocompatible device encapsulated by PI thin film has a high voltage (~4 V) and power density (~1.2 μW/cm^2), up to and exceeding levels relevant for practical use in implants, which has great potential for health/wellness monitors or non-biomedical devices.

2.3.4. Triboelectricity

Triboelectric nanogenerator (TENG) is another candidate battery-free power source for mechanical-to-electrical energy conversion. Two functional layers produce electrical charges by contact electrification and electrostatic induction during the contact of two surfaces with electron affinity, while the electrical charges between the two layers produces a voltage difference during the separation process [82–85]. There are four fundamental working modes of the TENG: vertical contact-separation mode, lateral sliding mode, single-electrode mode, free-standing mode (Fig. 4d) [71]. Contact-separation mode and sliding mode are common working modes for the flexible bioelectronics. However, for biomedical application, both TENG and piezoelectric devices must be driven by stable and regular mechanical motions.

2.3.5. Thermoelectricity

Unconstrained by mechanical motions, thermoelectric generators offer an alternative approach to harvest energy through Seebeck effect [86,87]. The power density of the thermoelectric generators is mainly determined by three factors: n- and p-type semiconducting elements (legs), array configuration of the legs and temperature difference between the skin and the ambient environment [87,88]. Commercialized inorganic bismuth telluride and antimony telluride based alloys are most common thermoelectric materials due to their high conversion efficiency at room temperature [88,89]. In the case of material determination, thickness and power generation are a pair of contradictory factors. An in-plane configuration leads to a decrease of power generation while ensuring thinner device thickness. Conversely, a cross-plane structure aligns with heat flow, resulting in improved voltage and power output at the expense of overall thickness. To resolve this contradiction, Rogers group recently proposed and demonstrate an architectural solution to this problem by developing 3D compliant and stretchable thermoelectric coils based on p- and n-doped single-crystalline silicon (200 nm) (Fig. 4e) [72]. This approach not only enables efficient thermal impedance matching but also multiplies the heat flow through the harvester, thereby increasing the efficiencies for power conversion. Particularly, the 3D flexible structure provides a multifold increase of the surface area, resulting in higher overall heat exchange capability and higher maximum power (2 nW). The continuous and stable power supply produced by thermoelectric generators is ideal for flexible bioelectronics.

2.3.6. Biofuel cell

Biofuel cells can generate electrical power by harvesting the redox biochemical reaction energy of body fluids and reaction electrode using enzymes and/or noble metal-based as catalysts [90,91]. The power density of the biofuel cell is mainly determined by three factors: available amount of chemical sources in body fluids, biochemical reaction rate and electron transfer efficiency. Stable operation is the biggest challenge for the biofuel cells, which is difficult because the amount of body fluid secretion is not the same as the environment changes, considering the device must continuously collect enough body fluids for biochemical redox, such as sweat [92]. Recently, Bandodkar and co-workers developed skin-interfaced microfluidic/electronic wearable sweat sensors, which can simultaneously monitor digital lactate and glucose signals through the biofuel cell-based electrochemical sensors (Fig. 4f) [73]. In particular, combination advantages of electronic and microfluidic functionality can complete the collection of sweat and real-time monitoring of sweat components more effectively.

2.3.7. Wireless power transfer

Wireless power transfer, including transmitting antenna and receiving antenna, can also act as supply energy or power to drive electronic devices without using other power source modules [16,37]. Rogers group reported a stretchable and implantable optoelectronic device powered wirelessly (Fig. 4g) [74]. The stretchable antenna harvested RF power through capacitive coupling between adjacent serpentine traces to reduce resonant frequency and therefore miniaturize the dimensions of the antenna (100-fold reduction at 2.34 GHz). Although the wireless power transfer system can achieve efficient transmitted power, the transmitting antenna must be powered by an external power source to drive the entire system.

3. Biosensors

The key requirements of biosensors are the integration of lightweight, conformal and biocompatible sensing components on body for in situ detecting. To meet the practical requirements of physiological signals sensing, as shown in Fig. 5, various wearable and implantable biosensors are designed to detect relevant physical and biochemical signals for healthcare monitoring and disease diagnosis, where the wearable biosensors (worn on body or integrated into accessories) function outside of bodies, and the implantable biosensors have the capability of healthcare monitoring in vivo [5,6,17,19]. This section is devoted on the biosensor categories classified based on different physiological signal types (biophysical or biochemical signals).

3.1. Physical biosensors

Physical biosensors are mainly to detect physical signals such as skin temperature, movement of the body or organs, and other physical phenomenon caused by organs in people's daily life. Our skin consists of epidermis, dermis, and hypodermis, and with embedded sweat glands, nerve endings, blood vessels, and muscle [15,16,19]. The outside epidermal layer is an ideal surface for health monitoring and diagnosis. In addition, implantable sensors to derive high-quality physiological signals from internal organs such as brain, heart, and blood vessels. A majority of physical biosensors being investigated are strain or pressure sensors, which are vital to motion monitoring. Even though conventional metallic strain gauges could be as thin as a few hundred micrometers, they are rigid, fragile, and not stretchable, which may limit their potentials in wearable and implantable applications [4,9]. On the other hand, the key challenge of a wearable pressure/force sensor is the

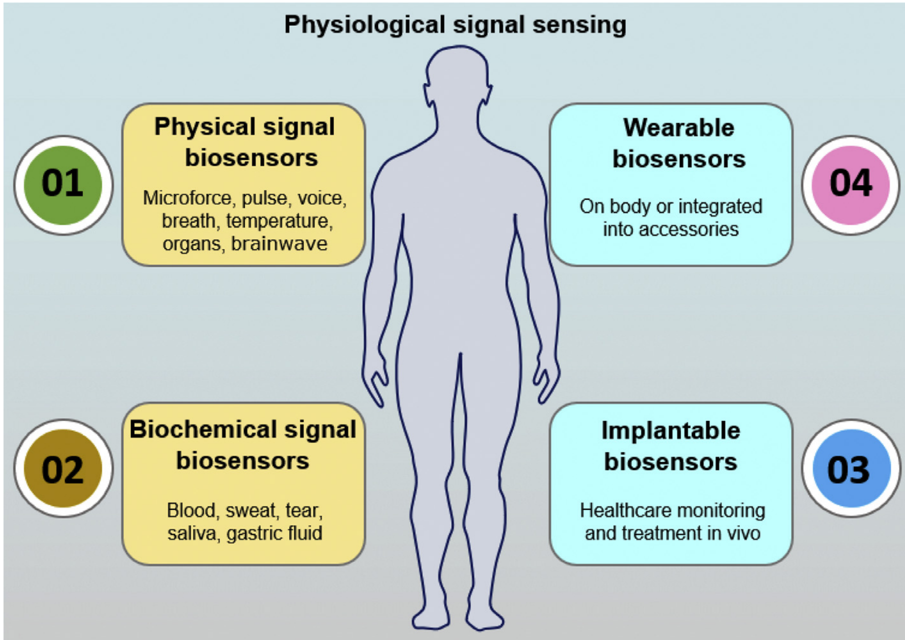

Fig. 5. Flexible biosensors to detect physiological signals.

demand of conformally attaching to our skin or the surfaces of internal organs and translating the physical mechanical deformation to digital signals [13,14]. Thus, flexible and stretchable physical biosensors are being actively developed to dynamically monitor the organ physical motion signal for healthcare.

3.1.1. *Wearable biophysical sensors*

Wearable biophysical sensors would enable a plethora of new applications in electronic skin, human activities monitoring, personal healthcare and human-machine interface [3,12,19]. Recent research interests of wearable biophysical sensors focused on movement and physical characteristics of the skin.

Wearable strain sensors (tension and pressure) based on the Ag nanoparticles (NPs) and carbon materials (carbon nanotubes or graphene nanosheets) composites on polydimethylsiloxane (PDMS) substrate using a simple and low-cost fabrication process have been recently reported (Fig. 6a, top) [93]. For the tension strain sensor, the composite junction resistance is consisted of two factors: the resistance between the Ag NPs (R′), and the resistance between the Ag NPs and carbon nanotubes (R″). This tension strain sensor could possess high sensitivity with tunable gauge factors (2.1−39.8), high stretchability of 95.8%, good linearity and excellent long-time stability. For the pressure sensor, the device was fabricated on a PDMS substrate with a 3D multi-layered Ag/graphene nanosheets structure (Fig. 6a, bottom) [94], showing that the interface contact resistance can be changed sensitively by the micro pressure (0.1 N). Based on sensing characteristics, these strain sensors are promising for human body motion capturing.

However, higher sensitivity is required for further device applications in the fields of real-time health monitoring, and structural design was employed to meet this requirement [100,101]. Recently, a high-performance wearable pressure sensor based on microstructured PDMS/Ag and rough polyimide (PI)/Au interdigital electrodes was used for real-time pulse wave monitoring (Fig. 6b) [95]. A voice recognition wearable device was reported (Fig. 6c) [96], which demonstrated superior sensitivity (1.80 kPa^{-1}), very low detectable pressure limit (0.6 Pa), fast response time (<10 ms), and high stability (>67500 cycles) for detection of feather-light pressures. In addition, a novel triboelectric sensor was fabricated to monitor the weak mechanical micromotion of the skin around the corners of eyes (Fig. 6d) [97]. These wearable biosensors provide an promising way for human physiological signals monitoring, disease diagnosis and health assessment, which provides a novel design concept for intelligent sensor technique and human-machine interaction.

To provide additional information on the changes in human skin, wearable multifunctional sensing platforms integrated with temperature, strain and humidity sensors have also been developed, which were able to simultaneously monitor subtle changes in skin temperature and strain during human activity [102,103]. The inorganic functional oxide film has rich physicochemical properties, thus the flexible or rigid device based on the oxide film has excellent adjustable properties [104–107]. In particular, Liao and co-workers designed and fabricated a stretchable VO_2/PDMS temperature sensor using transfer printing technology [58,108], demonstrating the possibility of tuning the properties of VO_2 thin films via external strain and expanding the application of VO_2 thin films in flexible and stretchable devices (Fig. 6e) [98]. In addition, due to VO_2 thin films are very sensitive to temperature as well as strain, they designed a flexible breath sensor and a dual parameter (temperature and strain) sensor with excellent sensing performance (Fig. 6f) [99,109]. These biosensors could be easily and conformally attached to human body and promising for prevention of apnea syndrome.

3.1.2. *Implantable physical biosensors*

Implantable biosensors to derive high-quality biosignals from internal organs such as heart, stomach, bladder and brain, are required in some cases rather than skin-mounted sensors [15,17,28]. Despite advances in device development, significant risks associated with solid, non-flexible systems remain. Therefore, flexible implantable devices to detect the biophysical signals of organs are currently research focus. Li and co-workers completed heartbeat monitoring in a live rat using a single zinc oxide (ZnO) nanowire (Fig. 7a) [110]. The ZnO nanowire has successfully converted the biomechanical energy from normal breathing or a

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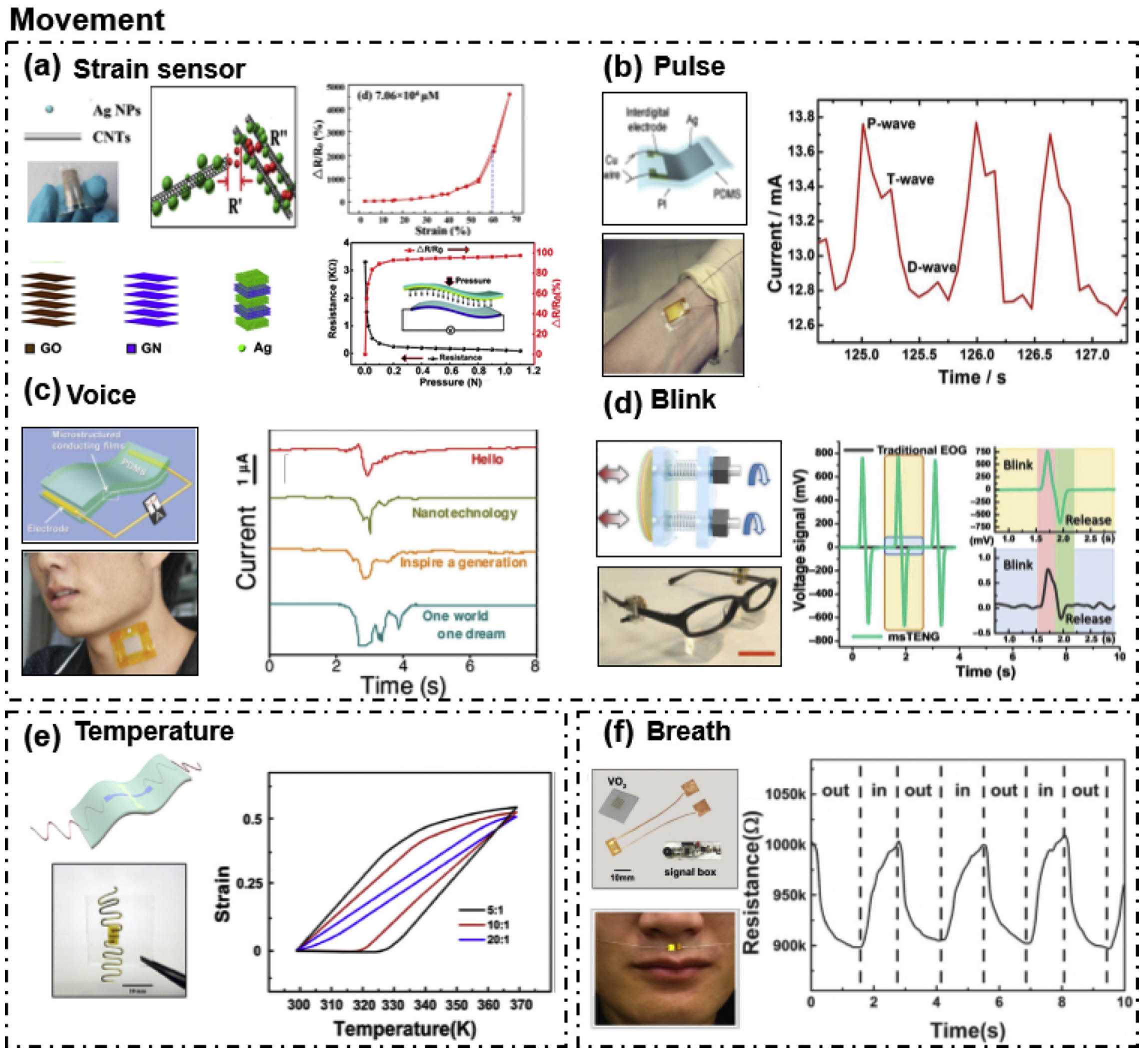

Fig. 6. Wearable biosensors on body for biophysical signal sensing. (**a**) Tension and pressure strain sensors [93,94]. (**b**) Real-time pulse wave monitoring [95]. (**c**) A wearable biosensor for voice recognition [96]. (**d**) A weak mechanical micromotion sensor [97]. (**e**) A stretchable VO_2/PDMS temperature sensor [98]. (**f**) A flexible breath sensor [99].

heartbeat into electricity, which presents a great potential towards implantable self-powered systems. In addition, a gastrointestinal (GI) motility sensing device based on lead zirconate titanate (PZT) ribbons for monitoring vital signals and ingestion within the GI tract was reported recently (Fig. 7b) [111]. The flexible device naturally unfolds and settles on the stomach lining in immediate juxtaposition with the mucosa, and provides instantaneous information on ingestion states in the GI tract. This biosensor may lead to the development of ingestible piezoelectric devices that might safely sense mechanical variations and harvest mechanical energy inside the GI tract for the diagnosis and treatment of motility disorders, as well as for monitoring ingestion in bariatric applications. Specifically, for underactive bladder (UAB), researchers presented a bio-stable actuator to empty the bladder by incorporating shape memory alloy components integrated on flexible PTFE sheets (Fig. 7c) [112]. The proposed actuator exhibits voiding percentage of up to 78% of the bladder volume in an anesthetized rat after only 20 s of actuation. The high sensitivity of this sensor to the filling status of the bladder provides a proof-of-concept for making a self-control system for future clinical application.

Monitoring real-time pressure and temperature within the intracranial provides essential diagnostic information for the treatment of traumatic brain injury. Rogers' group reported optical biosensor systems for monitoring of intracranial pressure and temperature (Fig. 7d) [113]. This flexible and bio-absorbable sensor consist entirely of inorganic materials, including silicon dioxide (~10 nm), single-crystalline Si NMs (250 nm) and adhesion layers of amorphous silica (~200 nm). This biosensor can be implanted in the intracranial space of a rat for monitoring intracranial pressure (ICP) and temperature (ICT), and results demonstrate the potential clinical utility of these systems. To obtain more comprehensive information about the brain, direct attachment of an electrode array on brain can be used to record electrophysiological signals and produce a high resolution map of the physiological signals. In general, according to working modes of sensing, the electrode array can be classified as resistive electrodes and capacitive electrodes. Recently, Lin group fabricated a stretchable conformal neural resistive electrode array using thermal release transfer printing method (Fig. 7e) [62]. Compared with stainless-steel screw (rigid) electrode, the stretchable electrodes exhibit a higher signal-to-noise ratio (SNR) and a relatively stronger response to light stimulus, indicating the stretchable neural electrode array can monitor steady-state visual evoked potential more efficiently. Since the direct contact brings concern of electrical safety and may be easy to cause irritation and allergic reaction, Lin group further developed an implantable capacitive electrode array with ultrathin dielectric

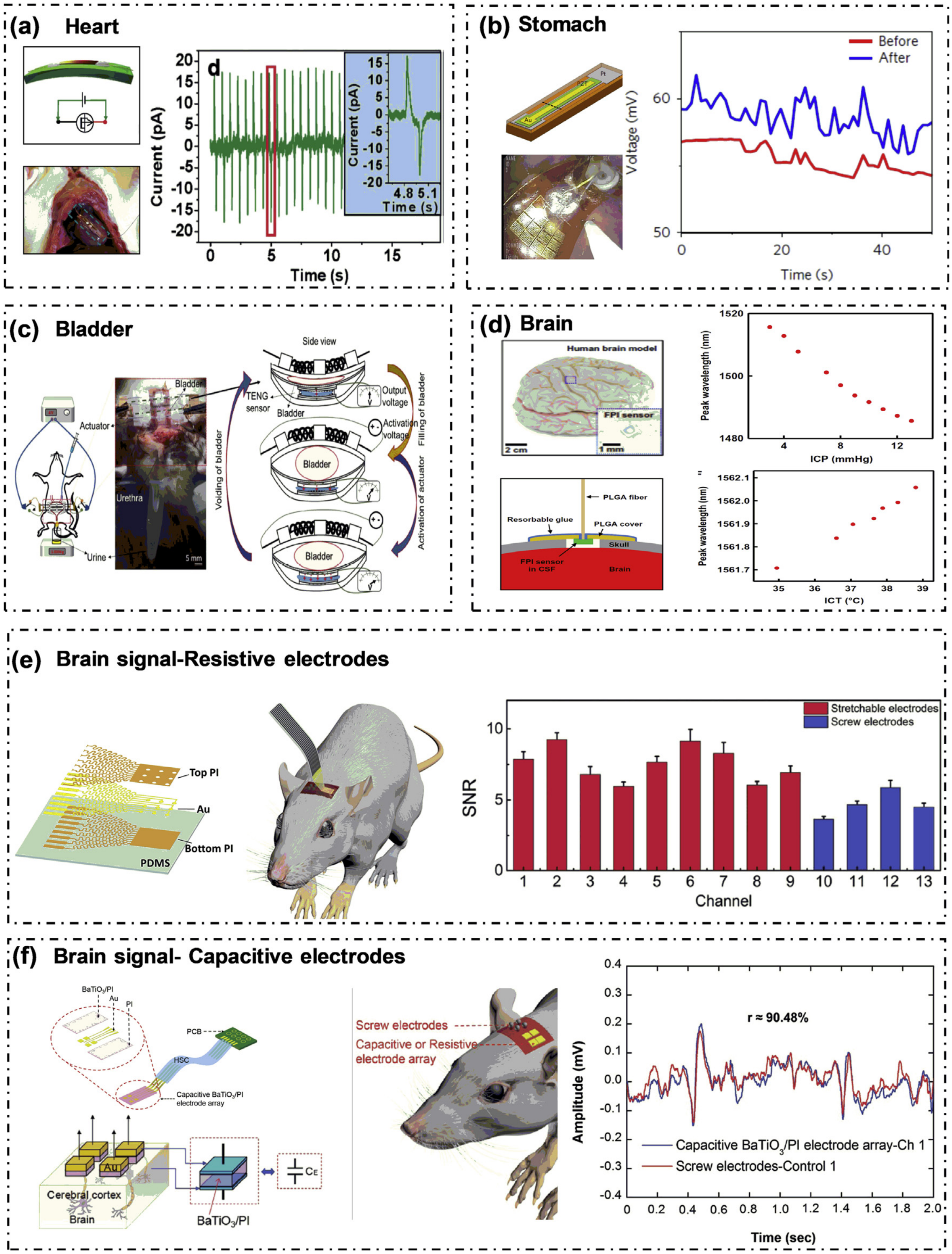

Fig. 7. Implantable biosensors for physical signal sensing in vivo. **(a)** Heartbeat monitoring in a live rat [110]. **(b)** A GI motility sensing device based on PZT ribbons [111]. **(c)** A self-control system for underactive bladder [112]. **(d)** Monitoring real-time pressure and temperature within the intracranial [113]. **(e)** A stretchable conformal neural resistive electrode array monitoring brain signal [62]. **(f)** A capacitive electrode array for in vivo recordings [114].

layer of the capacitive $BaTiO_3$/PI electrode array for electrocorticography signal recording (Fig. 7f) [114]. The monitoring results indicated that the signal quality of the as-prepared capacitive $BaTiO_3$/PI electrode arrays was comparable to the signal quality of conventional screw electrodes and resistive electrode arrays. Thus, this work broadens the scope of application of capacitive electrodes in neural signal acquisition.

3.2. Biochemical biosensors

Secreted human fluids, such as blood, sweat, tear, saliva and gastric fluid, can convey useful bio-information for health assessment. Hence, diagnostics based on body fluids can be an effective noninvasive monitoring method to provide insights into the health of a human [73,90]. However, despite its advantages, body fluids diagnostics has been limited to laboratory or hospital settings. A conventional electrochemical analyzing system is cumbersome as it typically comprises a working electrode, a reference electrode, a counter electrode and a reaction cell. Wearable applications cannot utilize conventional instruments which are bulky and rigid. Given this, the challenge of a wearable biochemical sensor is to achieve single step reaction analysis, instead of employing tedious procedures as commonly used in conventional sensing. For a wearable patch sensor, a stack-up layer by layer method is generally used to incorporate the sensing elements to realize multiple reactions in a single step [91,92]. Recently, a flexible organic reflectance oximeter array composed of organic light-emitting diodes and organic photodiodes was demonstrated to expand the usability and convenience of determining oxygen saturation in blood (Fig. 8a) [115], which senses reflected light from tissue to determine the oxygen saturation. The flexible reflection oximeter array with 2D spatial mapping capability monitored oxygen saturation on the forehead and with a mean error of 1.1%, which will aid in medical sensing applications such as 2D mapping of oxygenation in tissues, skin grafts, wounds, and transplanted organs. Moreover, a sweat sensor was fabricated with a stretchable microfluidic system and colorimetric sensor can provide noninvasive means for tracking physiologically relevant electrolytes, metabolites, and small molecules (Fig. 8b) [73,92]. The microfluidic sweat sensor serves as the foundations for light-weight, miniaturized, soft, battery-free, skin-interfaced technologies that combine biofuel cell sensors, colorimetric assays, NFC electronics, and soft microfluidics for simultaneous detection of lactate, glucose, chloride, pH, and sweat rate/loss, and then the collected information are sent wirelessly directly to the users. Long-term studies and correlation of data acquired by glucose and lactate sweat sensors with blood levels demonstrate the potential for noninvasive tracking of blood analyte concentrations.

Smart contact lens are capable of monitoring the physiological information of the eye and tear fluid, which could provide real-time, noninvasive medical diagnostics [50]. Recently, a soft, smart contact lens in which glucose sensors, wireless power transfer circuits, and display pixels to visualize sensing real-time signals are fully integrated using transparent and stretchable nanostructures (Fig. 8c) [116]. The integrated biosensors can operate reliably during mechanical deformations and monitor glucose levels in tears to indicate the diabetic condition in real time through a display with wireless operations. What's more, a graphene-based wireless sensor was integrated onto a tooth for remote monitoring of respiration and bacteria detection in saliva (Fig. 8d) [117]. The graphene/electrode/silk hybrid structure is transferred to biomaterials such as tooth enamel or tissue, and the biosensor is capable of extremely sensitive chemical and biological sensing, with detection limits down to a single bacterium and remote monitoring of pathogenic bacteria. In addition, recent studies reported an energy-harvesting galvanic cell (Mg–Cu system) for temperature sensing and wireless communication in a porcine model. The device delivered an average power of 0.23 $\mu W\ mm^{-2}$ of electrode area for an average of 6.1 days of temperature measurements in the gastrointestinal tract of pigs (Fig. 8e) [118]. This power-harvesting cell could provide power to the next generation of ingestible electronic devices for prolonged periods of time inside the gastrointestinal tract. Overall, biochemical sensors have revolutionized the standard of care for a variety of health conditions. Extending the ability and safety of these sensors could enable broad deployment of prolonged-monitoring systems for patients.

3.3. Problems faced by biosensors

Although flexible biosensors have achieved a great breakthrough compared to traditional rigid sensors, there are many challenges and some main problems need to be solved. The first challenge is how to calibrate the signal and accurately characterize the physiological information of the human body in different environments within the normal working range [8,92,118]. Second, how to ensure stable operation of the biosensors under harsh conditions requiring urgent solutions, since applying laboratory devices to complex or even harsh environments faces many limits, such as higher sensitivity requirements during exercise and device failure at high or low temperature [73,92]. Finally, the biggest challenge is how to integrate multiple biosensors (physical and chemical biosensors) to facilitate the convenient and comprehensive monitoring of physiological conditions. To solve these problems, more suitable functional materials and advanced manufacturing technologies are required to build.

4. Disease treatment

The surgery and medication are common approaches for diseases treatment. However, several rounds of surgery are associated with high cost, discomfortness and time commitment. In addition, oral or injectable drugs induce severe side effects and do not have targeted therapeutic effects [119,120]. Therefore, non-invasive, non-pharmacological, cost-effective, and convenient approaches are always desired for disease treatment. As an alternative of surgery and taking medication, targeted pharmacological therapy and non-pharmacological therapy provided by flexible bioelectronics are inevitable development trend for disease treatment.

4.1. Pharmacological therapy

A skin adhesive patch is the most fundamental and widely used medical device for diverse health-care purposes. Conventional skin adhesive patches have been mainly utilized for routine medical purposes such as wound management, fixation of medical devices, and simple drug release [121]. Currently, with recent advances in nanofabrication, nanomaterials, and flexible electronics, the skin adhesive patch has evolved into a smart multifunctional device by incorporating core functions of bulk medical instruments within a thin flexible adhesive patch [122,123]. This part focus on drug delivery for ubiquitous personalized health care and development of the medical drug-delivery devices.

Gu and co-workers reported a novel glucose-responsive insulin delivery device using a painless microneedle-array patchcontaining glucose responsive vesicles with insulin and glucose oxidase enzyme (Fig. 9a) [124]. The matrix can undergo structural transformations (shrink, swell, dissociate) regulated by glucose concentration changes, leading to glucose-stimulated insulin release. This synthetic glucose-responsive device, using a hypoxia trigger for regulation of insulin release, builds a “closed-loop” insulin delivery system, which provides a desirable way of regulating glycemia with potential improvements in glycemia as well as quality of life and health in diabetics. To improve the efficiency, Wang group recently developed a biomechanical-energy-powered TENG-driven electroporation system to deliver intracellular drug effectively (Fig. 9b) [125]. This device promotes the increase of plasma membrane potential and membrane permeability to deliver exogenous materials into different types of cells with delivery efficiency up to 90% and cell viability over 94%, and this high-efficiency electroporation drug delivery system has great potential for future disease treatment.

To further expand the application of drug delivery, Li and co-

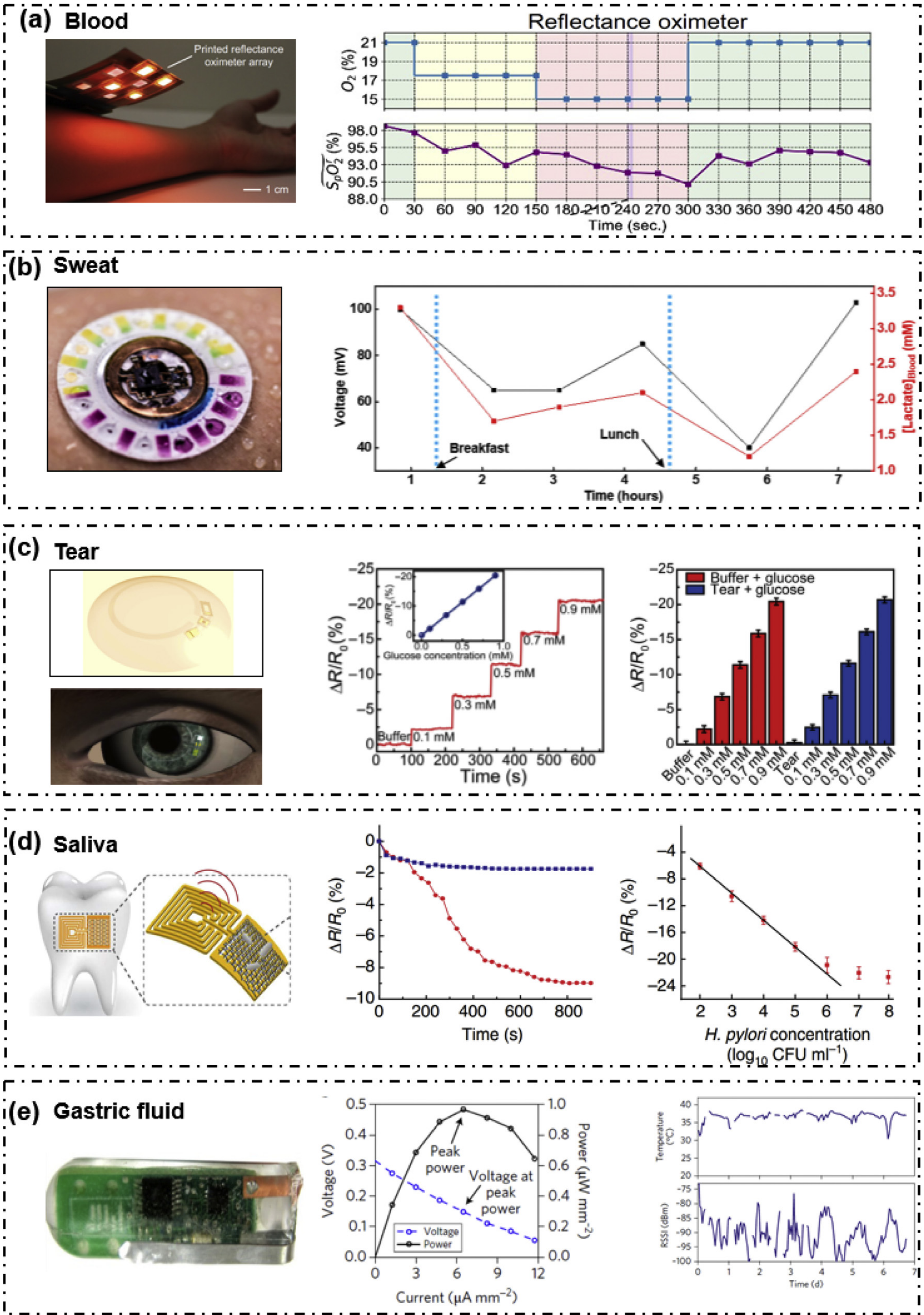

Fig. 8. Biochemical signal sensing of body fluids. **(a)** A flexible organic reflectance oximeter array [115]. **(b)** A stretchable sweat sensor [73]. **(c)** A soft and smart contact lens for glucose sensing [116]. **(d)** A graphene-based wireless sensor on tooth for bacteria detection in saliva [117]. **(e)** Ingestible electronics for temperature sensing and wireless communication [118].

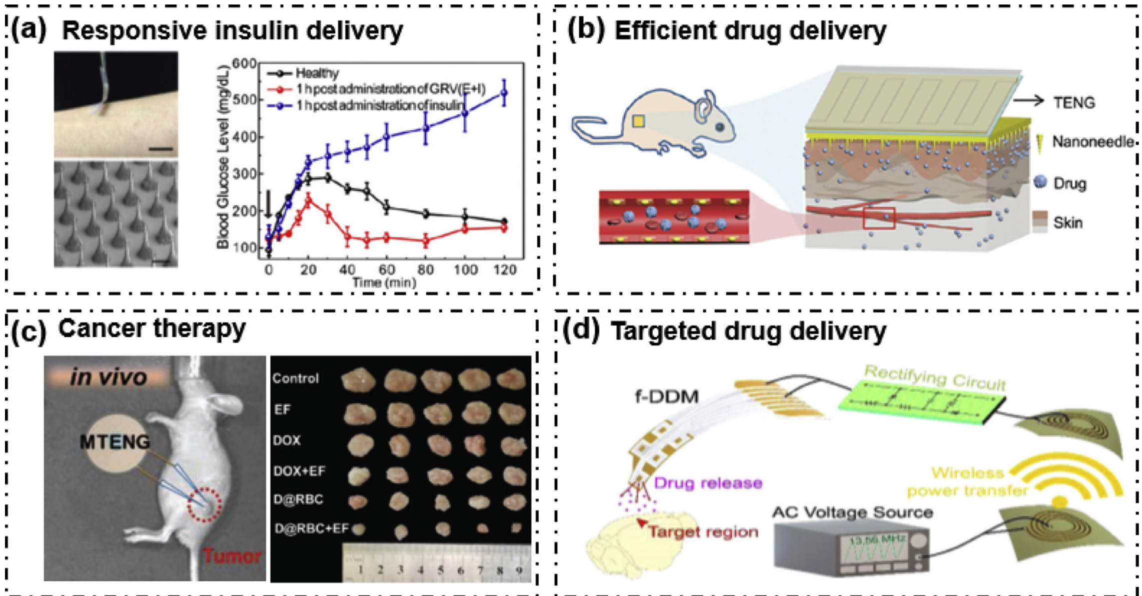

Fig. 9. Pharmacological drug delivery system. (a) A glucose-responsive insulin delivery system [124]. **(b)** A TENG-driven system for effective intracellular drug delivery [125]. **(c)** Drug delivery for cancer therapy [126]. **(d)** A targeted drug delivery system [127].

workers reported a nanogenerator-controlled drug delivery system (DDS) for cancer therapy (Fig. 9c) [126]. Doxorubicin-(DOX-) loaded red blood cells (RBCs) are employed as the anti-tumor DDS and the TENG output, up to 70 V after implantation, can remarkably increase DOX release. The EF withdrawal can stop the increased release, resulting in a controllable release pattern. The distinguished therapeutic effect is highly promising to be applied in the clinic. In addition, Lee group reported a flexible drug delivery microdevice (f-DDM) for controlled administration on the curved organ surface (Fig. 9d) [127]. The f-DDM consists of freestanding gold membranes over the multireservoir array and the electrochemically soluble gold sealing can precisely regulate the drug release. The localized treatment would minimize the side effects of the drug with lower dosage and this system would contribute to the development of precision medicine. Although the effective treatment can be obtained by drug delivery system, the side effects of the drugs can not be ignored.

4.2. Non-pharmacological therapy

Currently, several promising non-pharmacological treatments including current stimulation, laser and thermal treatments have been developed and are gradually applied in clinic for disease treatment [128–130], such as cardiac pacing, nerves stimulation, cell proliferation and tissue engineering.

Neuromodulation of current stimulation is a non-destructive and reversible therapeutic strategy, which can manipulate influencing neurophysiological signals or body functions by stimulating through the neural networks to achieve therapeutic purpose. Rogers' group reported a wireless bioresorbable electronic system for neuroregenerative therapy (Fig. 10a) [37], which is driven by radio frequency harvesting power. All components of the device are degradable materials, including Mg, poly lactic-co-glycolic acid and silicon dioxide. This work demonstrated that electrical stimulation of injured nerve tissue proximal to the site of repair can enhance and accelerate functional recovery. In order to get rid of external power restrictions, Wang group reported an implanted vagus nerve stimulation system that is battery-free and spontaneously responsive to stomach movement (Fig. 10b) [29]. The VNS device was attached to the stomach wall of rats and could generate biphasic electric pulses in responsive to the peristalsis of stomach. The electrodes were directly connected to the vagus nerve to reduce food intake and achieve weight control. In particular, the device can work stability and exhibit excellent biocompatibility without any signs of side effects from the whole blood and chemical analysis. This self-responsive and real-time peripheral neuromodulation mechanism may be more effective for achieving therapeutic purpose. As another example of nerve stimulation, Fabien and co-workers developed targeted epidural electrical stimulation neurotechnologies, which enabled restored voluntary control of walking in individuals who had sustained a spinal cord injury (Fig. 10c) [130]. This work indicated that neurotechnologies can provide the usability features to support rehabilitation in clinical settings and use in the community.

Electric field can induce a non-invasive biological effect named electrotrichogenesis (ETG). Alternating electric field in the range of 0.1–10 V/cm and frequencies of <15 Hz are commonly used, which imposes negligible tissue damage. ETG could enhance the influx of calcium ions into the dermal papilla cells via voltage-gated transmembrane ion channels, facilitate adenosine triphosphate (ATP) synthesis in mitochondria, activate protein kinases, and stimulate protein synthesis and cell division. For example, Wang group developed an efficient electrical bandage for accelerated skin wound healing (Fig. 10d) [131]. The device can generate a discrete AC electric field directly by converting the kinetic energy generated from a rat breathing. The therapeutic effects for wound healing were attributed to the electric field which promoted fibroblast migration, proliferation, and transdifferentiation. The results bring an effective therapeutic strategy to chronic disease treatment. To further apply the electric field in tissue repair and regeneration, Wang's group developed a universal motion-activated omnidirectional *m*-ESD for accelerated hair regeneration on SD rats and nude mice via random body motions (Fig. 10e) [132]. After the device was applied, higher hair follicle density and longer hair shaft length were observed on Sprague–Dawley rats. Particularly, this device can alleviate hair keratin disorder, increase the number of hair follicles, and promote hair regeneration on genetically defective nude mice, which is attributed the increasing secretion of vascular

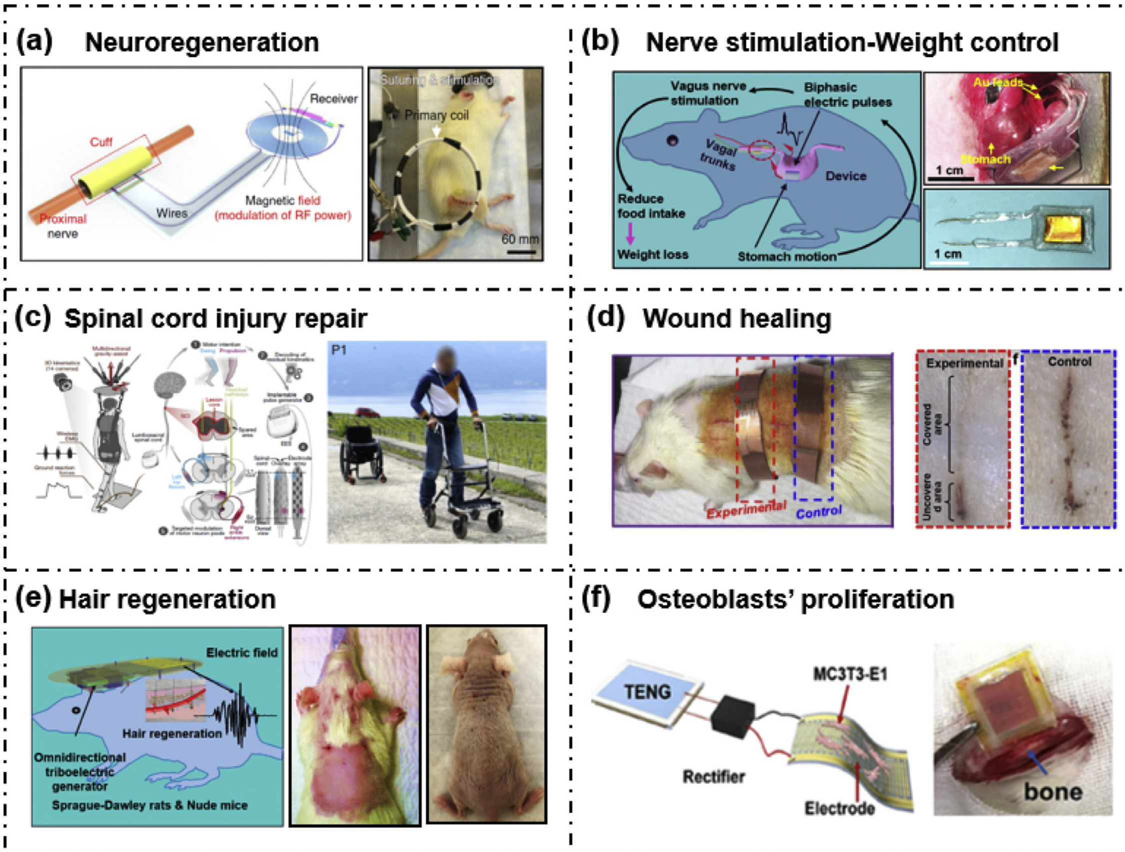

Fig. 10. Non-pharmacological therapy. **(a)** A wireless bioresorbable current stimulation system for neuroregenerative therapy [37]. **(b)** An implanted vagus nerve stimulation system for weight control [29]. **(c)** Current stimulation for spinal cord injury repair [130]. **(d)** An efficient electrical bandage for wound healing [131]. **(e)** A motion-activated device for hair regeneration [132]. **(f)** An implanted system for osteoblasts' proliferation and differentiation [133].

endothelial growth factor and keratinocyte growth factor. This work revealed physiologically appropriate alternating electric field plays a key role in the field of regenerative tissue engineering. Similarly, Li and co-workers proposed a flexible and implantable electrical stimulator, which consisting of a TENG and an interdigitated electrode (Fig. 10f) [133]. The results showed that this stimulator significantly promoted osteoblasts' attachment, proliferation and differentiation, and promoted intracellular Ca^{2+} secretion. This work provided a promising way for clinical therapy of bone fracture and bone remodeling after bone transplantation. Due to the non-invasive nature, powerful diagnosis capabilities and good curative effect, more and more patients will rely on implantable medical electronic devices, which show great potential application in the future.

5. Conclusion and outlook

This review summarizes advanced integration strategies of flexible bioelectronics, including novel materials, sensing modalities, stretchable circuits and power sources, highlighting the recent progress of flexible electronics in the field of physiological signals sensing and disease treatment. These developments establish solid foundations for new classes of multifunctional flexible bioelectronics, which will promote further integration of human body with devices and accelerate the construction of powerful and intelligent healthcare platforms.

Despite the achieved progress in this field are encouraging, considerable challenges still remain. Flexible and hybrid integrated sensor arrays, including physical and biochemical sensors, are required for simultaneous multiplexed in situ signals analysis. Given the complexity of physiological signals, on-site signal processing circuitry and sensor calibration mechanisms for accurate analysis are in ever-increasing demand to ensure the accuracy of measurements. In addition, function-autonomous bioelectronics with intelligent health database and powerful functions are expected to proactively implement health maintenance from physiological signal detection, disease prediction, disease diagnosis to disease treatment. It is foreseeable that with the advent of the era of flexible bioelectronics and artificial intelligence, intelligent flexible bioelectronics will become a critical player in next-generation electronics.

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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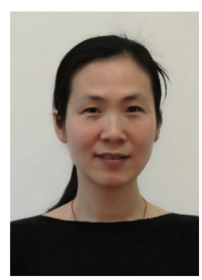

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