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Multimodal sensing and therapeutic systems for wound healing and management: A review

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A B S T R A C T

Wounds especially chronic ones significantly affect the quality of patients' life and present a severe financial burden for the healthcare industry. Timely and effective management of wounds, such as diagnosing wound parameters, treating various wound symptoms, and reducing infection at the wound noninvasively, is very important for accelerating wound healing and relieving patients' pain. Recent years have seen significant efforts dedicated to developing technologies for monitoring various biomarkers vital to the wound healing process including temperature, pressure, pH, and the infection status to assist with the diagnosis and treatment of wounds, as well as advanced wound therapies such as on-demand and local drug delivery. This review paper introduces recent progress on multimodal sensing and therapeutic systems for wound healing. Specifically, we focus on physical sensing (temperature, moisture, pressure, and strain), chemical sensing (pH, uric acid, and cytokine), as well as therapeutic systems for wound management (active drug delivery systems based on external stimulations and non-drug stimulations). In addition, leveraging advanced analytic techniques, i.e., machine learning and deep learning, for data-driven assessment and management of the wound healing process has been discussed.

1. Introduction

As the largest organ, skin plays important roles in protecting human body from environmental pathogens and chemicals as well as in preventing dehydration and thermal shock [1–3]. Due to various factors including physical damage from daily activities, traumatic events and burns, long-term exposure to excessive loading, and diseases, the integrity of the skin tissue, however, can be broken or can generate defects, which is addressed as a wound. Underlying conditions such as diabetes and ischemia can alter the skin properties and make it more susceptible to physical impacts [4–8]. When a wound cannot be repaired normally and completely, it is defined as a chronic wound (such as diabetic foot ulcers and pressure injuries), which sustains disordered repairing processes and fails to resolve after 30 days [9–11]. Chronic wounds present grave health burdens for individuals afflicted with the condition, and improper treatment can lead to limb amputations or even premature deaths. Meanwhile, they present a severe financial burden for the healthcare industry [12], costing over $20 billion annually and affecting 5.7 million people in the U.S. [13]. Due to the aging of the population and the increasing incidence of chronic diseases, the prevalence of chronic wounds and healthcare costs are expected to grow [14].

Wound healing is a dynamic and continuous process, which can be divided into four overlapping stages: (1) hemostasis: stopping bleeding at the injured area that is then infiltrated by immune cells removing debris and pathogens [15,16], (2) inflammation: removing the contaminating microorganisms and debris [17,18], (3) proliferation: filling the wound defects and covering the wound surface as fibroblasts proliferate [19,20], and (4) remodeling: strengthening the wound tissue as capillaries merge into stable vessels [21]. Once wounds progress through all the four integrated stages, the full recovery of the structural and functional integrity of the skin will be achieved. However, wound healing could be delayed by persistent inflammation or repeated infections, which eventually results in the chronicity of wounds [22]. The factors affecting wound healing could be classified into two categories: systemic factors and local factors. The systemic factors are related to the overall health state of the individual, including age, chronic diseases,

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nutritional status, and vascular insufficiency. The local factors are directly related to the characteristics of the wound itself, including desiccation, infection, external pressure, and trauma [17,23]. Some major injuries or underlying conditions such as diabetes could negatively impact the activity of the cells at the injury site and lead to impaired wound healing [4–8]. An approach to effectively manage wound healing is crucial to help patients recover from chronic pain and reduce the burden on the public healthcare system.

Current wound care decisions are usually based on guidelines regarding the type and location of the wound, underlying conditions, and visual inspection by healthcare providers [24]. However, this strategy has not been very effective and chronic wounds are the leading cause of limb amputation. The lack of detailed knowledge about the wound environment has become one of the challenges in clinical wound care for making better decisions and personalization of the treatments [25,26]. Recent advances in wearable electronics and intelligent patches have attracted much attention for monitoring the surrounding environment of wounds due to their advantages including flexibility [27,28], stretchability [29,30], real-time monitoring, noninvasiveness, high sensitivity [31,32], and high stability [33,34]. For example, biochemical and physiological properties such as potential hydrogen (pH), glucose, inflammatory factors, and temperature, which are correlated to the wound status, have been monitored *in situ* using wearable patches. Specially, during the Covid-19 pandemic, the cancelation in outpatient clinics has driven the development of telemedicine for wound treatments and self-changing wound dressing [14]. For effective personalization of treatments, advanced drug delivery tools are needed to allow on-demand and local delivery of therapeutics at the desired time [35]. In addition, considering the multifactorial pathologies causing impaired wound healing, monotherapies have not been successful in inducing tissue repair [36]. Therefore, wearable bandages should allow the delivery of multiple drugs with independent kinetics. Furthermore, integrating advanced data processing techniques (e.g., a machine-learning framework) with sensing and actuation will highly accelerate wound healing and promote the revolution in the wound treatment.

Much recent groundbreaking work has been dedicated to fully monitoring and understanding the wound healing process and effectively treating the wound. This review paper is meant to provide an overview of recent efforts in wound monitoring and management. The review is organized in the following manner: First, physical sensing will be detailed. Then, studies on chemical sensing will be presented, followed by wound management. Finally, advanced analytical techniques including machine learning and deep learning for wound assessment and management will be discussed.

2. Physical sensing for wound monitoring

Physical parameters of the wound site are important indicators of the wound progression status and therefore could serve as significant inputs for wound treatment. In this section, we will review physical sensing of wounds including temperature, moisture, pressure, and strain.

2.1. Temperature sensing

Temperature is one of the most commonly recorded physical markers in the body because rates of many enzymatic reactions are temperature dependent. In particular, temperature is related to the inflammation and infection states of wounds [37], and has been adopted as a classic sign of the Clinical Signs and Symptoms Checklist (CSSC) to standardize the assessment of chronic wounds worldwide [38]. The range for the temperature at the skin is from 31.1 °C to 36.5 °C. At the wound site, a prolonged temperature increase of at least 1.11 °C could be due to infections and metabolic activity changes. Specifically, a peri-wound temperature increase of 3 °C to 4 °C has been observed to be correlated with signs and symptoms of infection within 40 participants that have chronic leg ulcers [39]. In the cases with clinically diagnosed wound infection, temperature differential between the wound and healthy skin increased to 4–5 °C, and returned to 0.8–1.1 °C after an adequate treatment with antibiotics [40]. Thus, the peri-wound skin temperature could be used as a useful reference for monitoring the infection symptoms and treatment status.

Traditional temperature measurement methods, including those through an examiner's hand during physical assessment and through conventional mercury or electronic thermometers, suffer from drawbacks including limited diagnostic accuracy and difficulty in being attached to the wound surface. Recent advances in flexible electronics and wireless data communication have enabled flexible temperature sensors suitable for real-time, noninvasive monitoring of temperature changes during the wound healing process. In addition, stretchable temperature sensors for on-skin electronics are realized by utilizing platinum (Pt) nanofiber networks [41], elastomeric reduced graphene oxide (rGO)/polyurethane (PU) composite fibers [42], and gold (Au)-coated conductive nanomeshes [43]. Numerous methods and various thermal-sensitive materials are used for measuring temperature (Fig. 1A), such as conductive polymer ink (e.g., PEDOT:PSS [44–47]), carbon-based nanomaterials (e.g., carbon nanotube (CNT) forest [48] and reduced graphene oxide hydrogel (rGOH) [49]), and their composites (carbon nanotube/SnO_2 [50] and MXene/Fe_3O_4/graphene [51]). Also, temperature sensors could be made transparent by using materials like liquid crystals [52], ionogels [53] and hydrogels (Fig. 1B) [54]. Many common flexible temperature sensors are based on the principle of electrical resistance changes in response to temperature. The temperature sensitivity is defined by the temperature coefficient of resistance (TCR):

$$TCR = \frac{\Delta R/R_0}{\Delta T} \times 100\%, \quad (1)$$

where R_0 is the initial resistance of the temperature sensor, ΔR is the total resistance change upon temperature variation, ΔT [44,45,51,55]. For example, a flexible integrated sensing platform (FISP) composed of a flexible temperature sensor chip (FSC) and a controlled printed circuit board (CPCB) were used to monitor local temperature [56]. Conductive hydrogels were used to sense temperature and, in the meanwhile, could promote the healing of the infected chronic wounds with electrical stimulation [57]. More recently, a flexible wound healing system was developed for real-time, noninvasive wound temperature monitoring (Fig. 1C–E) [58]. The hardware was designed in a Band-Aid shape with a double-layer structure: an upper flexible temperature-sensing layer consisting of the temperature sensor and circuits, and a lower collagen chitosan dermal equivalent for skin regeneration. An app on a smartphone was used to receive, display, and analyze the measured wound temperature in real time. Furthermore, it was applied to a pig skin wound model to measure the temperature change during the entire wound regeneration process, which revealed three main phases of temperature fluctuation: the rising phase (below 39 °C), the plateau phase (39–39.5 °C), and the falling phase (below 39 °C), which were accompanied by significant biological events, including inflammatory cell infiltration and wound healing. The development of flexible temperature sensors for wireless, real-time wound monitoring and the correlation of temperature measurements to the wound progression status represent a significant advance in wound healing.

2.2. Moisture sensing

Moisture has been treated as an essential part of the wound healing environment. Maintaining an appropriate level of moisture at the interface between a wound and a dressing is critical for effective wound healing. This is because a wet wound environment could possibly lead to maceration and wound deterioration, while too little moisture will dry out the wound and impede healing [59,60]. Effective management of wound moisture can reduce the time of wound healing and the

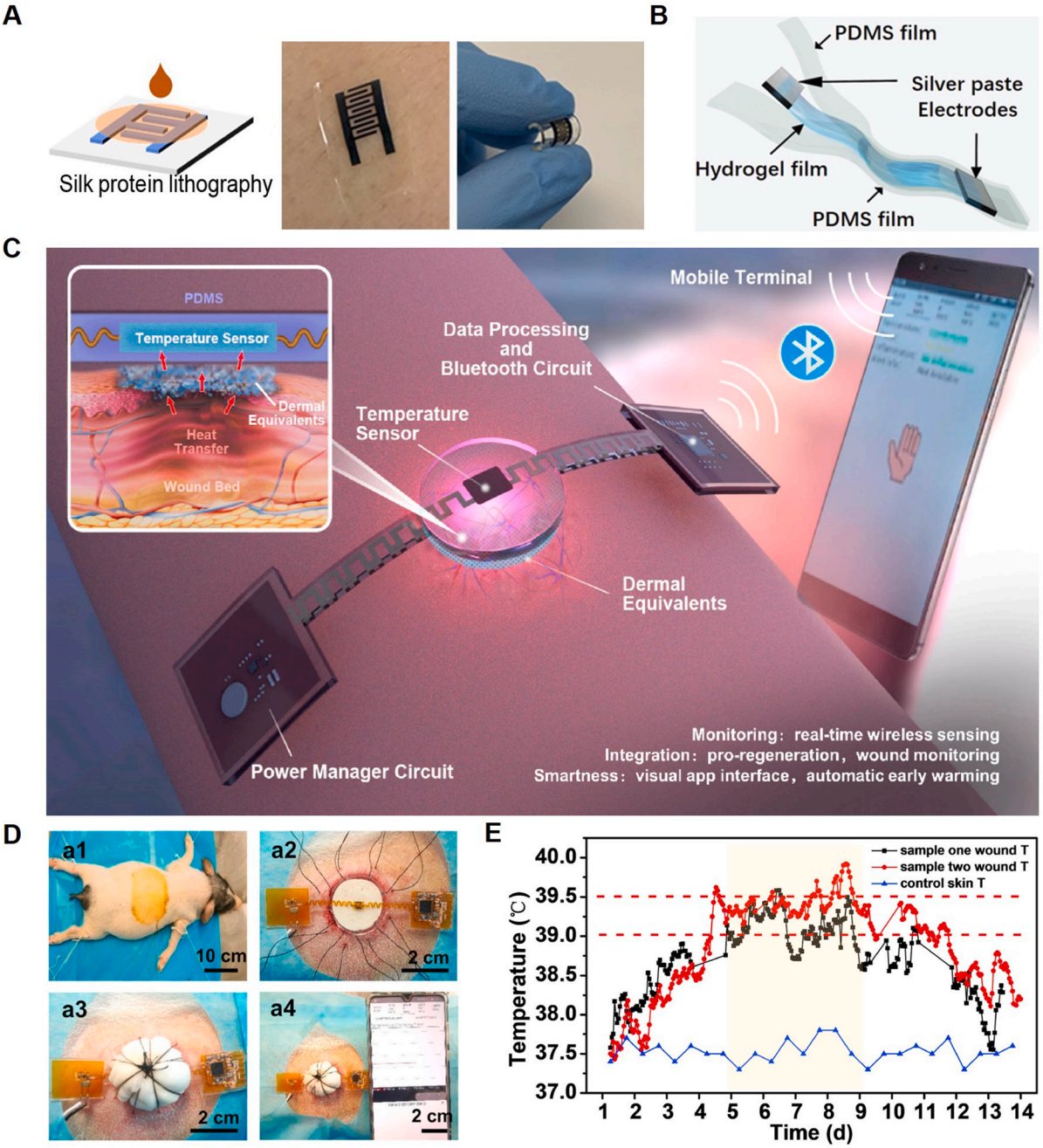

Fig. 1. (A) A flexible temperature sensor composed of a silk fibroin substrate, photolithographically micropatterned sericin/PEDOT:PSS electrodes and a sericin/rGO temperature sensitive layer [44]. (B) A stretchable temperature sensor based on a transparent hydrogel thin film [54]. (C) Schematic illustration of the application scenario of a flexible wound healing system for real-time, noninvasive wound temperature monitoring [58]. (D) Pig full-thickness incisional wound model and system implantation for the system shown in (C) [58] (E) Plots of temperature vs. time for two weeks' wound healing [58].

frequency of dressing change, which in turn reduces wound care time and improves patient comfort [61]. Achieving the desired moisture level in the wound environment had relied on appropriate clinical judgement and dressing selection from an extensive range of dressing types and materials, which could be subjective [62].

There has been a significant effort in the research community to develop wearable devices to assist with objective assessment of the wound status for wound care professionals to perform moist treatment of wounds. In particular, a moisture sensor has been developed to monitor moisture levels in real time [63], which was subsequently commercialized by Ohmedics (Ohmedics Ltd, Glasgow, UK) as the WoundSense™ sensor (Fig. 2A) [64]. It is a sterile, disposable moisture sensor that is placed on the wound within the dressing, thereby allowing monitoring the moisture status without affecting the dressing [64]. The sensor detects the moisture content of the wound through low-current electrical impedance measurements, which are conducted via a pair of silver chloride electrodes printed on a flexible, biocompatible polymer. A meter attached to the sensor provides an easy-to-understand five-drop moisture scale, where a reading of 1 means the dressing is very dry, 5 means the dressing is very wet, and a reading of 3 indicates ideal moisture conditions for healing [64]. Fig. 2B shows that as the mass of liquid in the dressing falls below 50% of the initial value, the impedance measured by the electrodes begins to increase [63]. More recently, a moisture sensor based on carbon-zinc (Zn) and carbon-manganese dioxide (MnO_2) was used to detect moisture that is related to the absorbing capacity of the dressing to inform the frequency of dressing

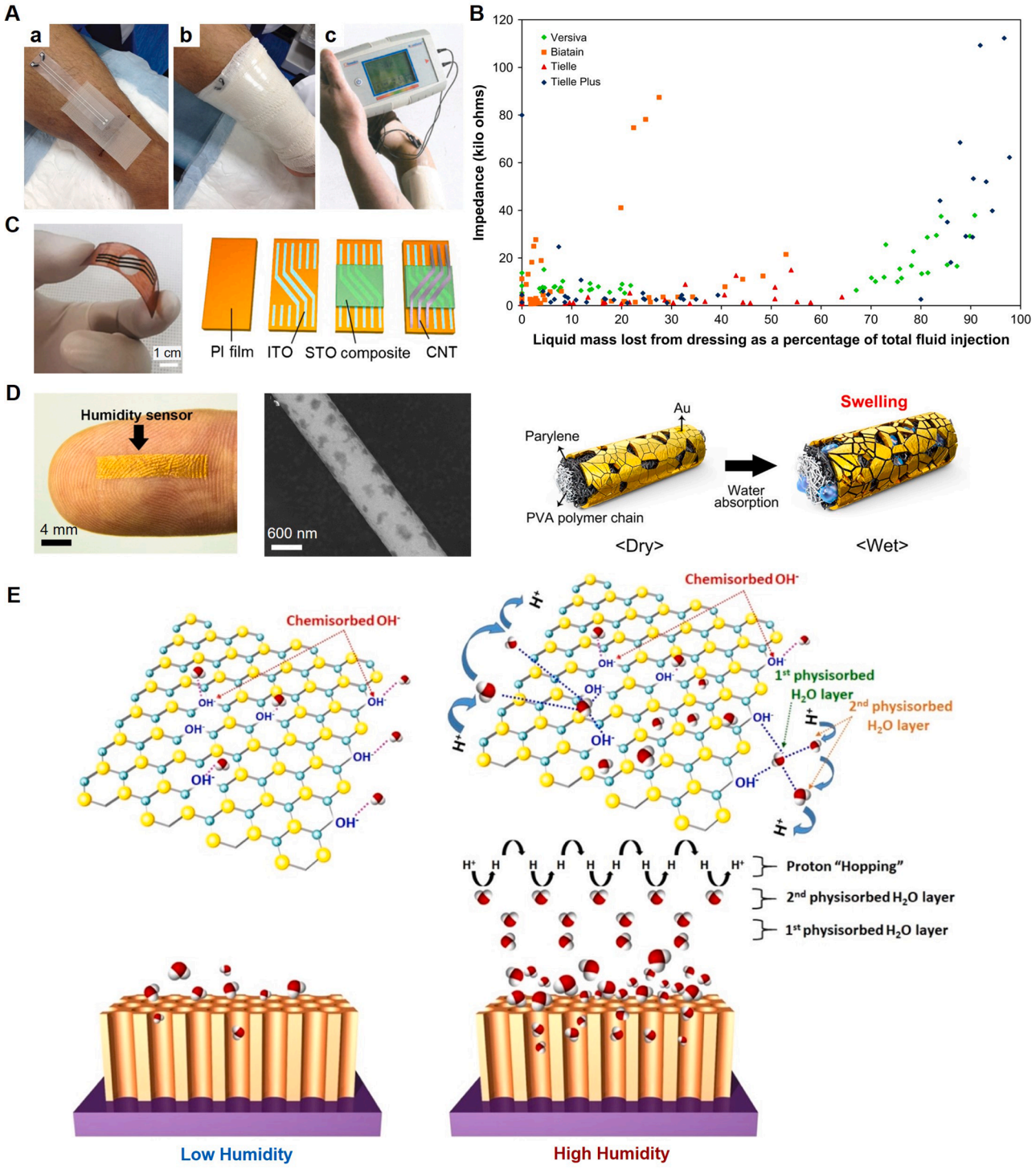

Fig. 2. (A) WoundSense sensor for moisture monitoring in the wound bed: (a) sensor underneath dressing, (b) sensor after dressing, and (c) measurement with a WoundSense meter [64]. (B) Relationship between the percentage of liquid lost from the dressing and the measured impedance via paired silver/silver chloride electrodes embedded in the dressing [63]. (C) Transparent humidity sensors with perovskite-structured $SrTiO_3$ (STO) composites [73]. (D) A breathable nanomesh humidity sensor composed of parylene C-encapsulated PVA polymer chains and a discrete gold surface [76]. (E) Schematic illustration of the humidity sensing mechanism including the chemisorption of hydroxyl ions (OH^-) at low humidity conditions, and the physisorption of water molecules followed by proton hopping at high humidity conditions [79].

change [65].

In addition, various flexible humidity sensors have been developed, which can be potentially considered for applications in human healing. The sensors are based on the mechanism that water molecules alter the electron transfer pathway of sensing materials and/or form hydrogen bonds with sensing materials [66]. Most humidity-sensitive materials in flexible humidity sensors are composites, such as polyvinyl alcohol (PVA)/MXene nanofibers [67], cerium oxide/graphitic carbon nitride (CeO_2/g-C_3N_4) [68], palladium (Pd)-modified HNb_3O_8 nanosheets [69]. Humidity sensors could also be made transparent by using cellulose nanofibers [70] and silk fibroin [71]. The carbon-related materials (e.g. carbon nanotubes (CNTs) [66,72,73], graphene [74] and graphene

oxide [75]) are commonly incorporated into composite materials to increase their conductivity and sensitivity, as shown in Fig. 2C. A breathable nanomesh humidity sensor that can provide good conformal contact on human skin was reported by using biocompatible polymer nanofiber (PVA polymer chains encapsulated by Parylene C) and a discrete gold layer (Fig. 2D) [76]. Stretchable, transparent humidity sensors are further implemented for the applications of body-attachable (skin-attachable) electronics by using bilayer double-network hydrogels [77], rGO/PU composites, and WS_2 semiconducting films [78]. Transition metal dichalcogenides, such as WS_2 and MoS_2, are considered promising candidates for humidity sensing materials because their inherent defects in the two-dimensional (2D) layered structure provide abundant active sites for water molecule absorption [79,80]. The humidity sensing mechanism of transition metal dichalcogenides are shown in Fig. 2E. Under low humidity conditions, water molecules are dissociated ($H_2O \rightarrow H^+ + OH^-$) and the generated hydroxyl ions (OH^-) are chemisorbed on the defect sites of the MoS_2 surface. In high humidity environments, additional water molecules are physisorbed on the

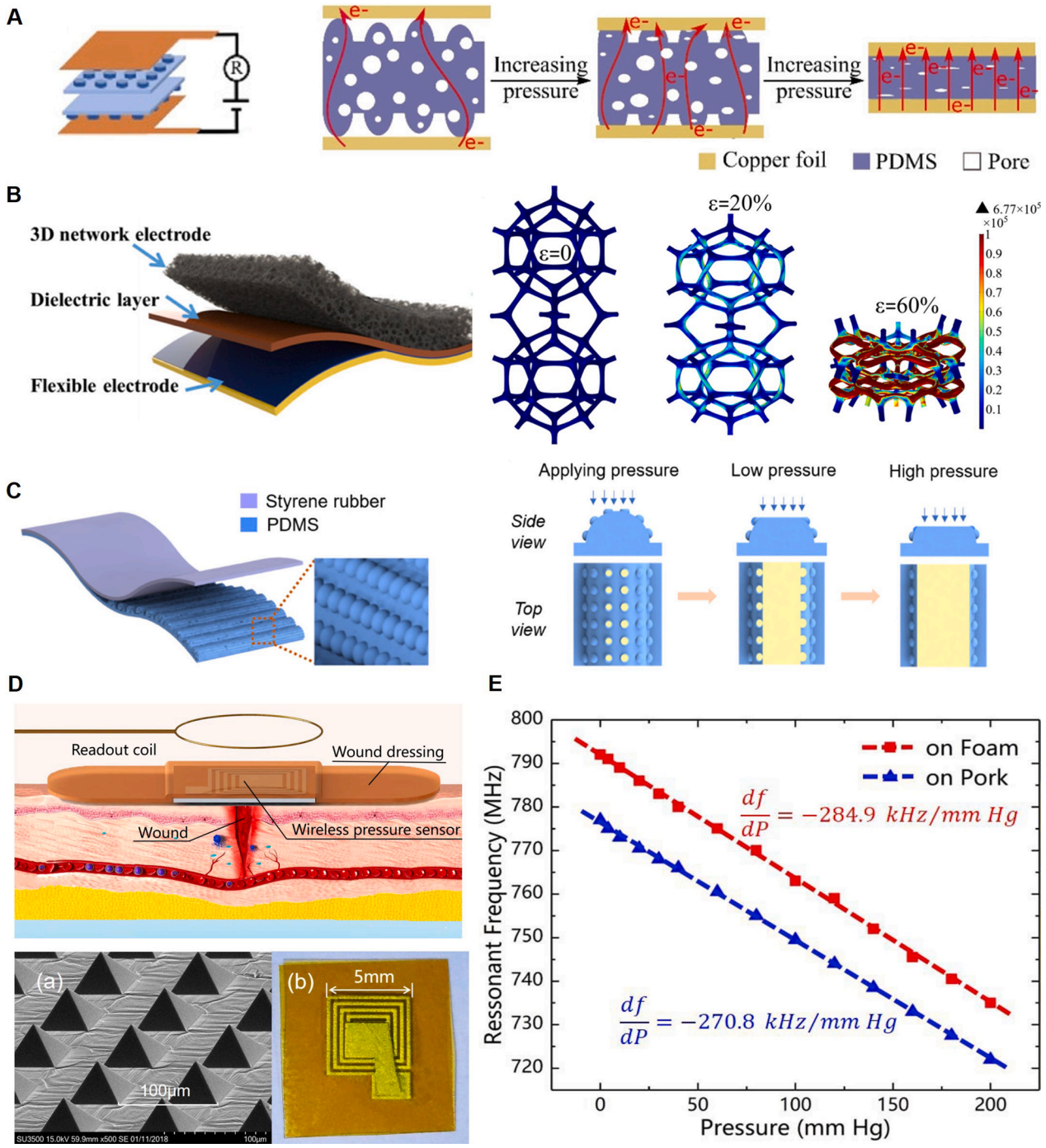

Fig. 3. Schematic illustrating the structure and sensing mechanism of (A) A piezoresistive pressure sensor with PDMS/MWCNTs composites patterned with microstructures [94], (B) A capacitive pressure sensor consisting of MXene nanocomposite dielectric and a 3D network electrode (3DNE) [98], and (C) A triboelectric pressure sensor composed of styrene butadiene rubber (SBR) and patterned poly(dimethylsiloxane) (PDMS) [102]. (D) An LC (inductor-capacitor) pressure sensor consisting of a pyramidal PDMS layer and a spiral inductor for wireless wound monitoring [105]. (E) Measured resonant frequency vs. applied pressure when the LC-sensor-embedded bandage was attached to a pork and a foam, respectively [105].

hydroxyl ions and then excess protons diffuse through hydrogen bond networks between adjacent water molecules. The proton hopping process, known as the Grotthuss mechanism, might contribute to increased conductivity and higher sensitivity of the humidity sensors at high humidity levels [79]. Integrating the developed moisture/humidity sensors with other types of sensors for wound monitoring would provide important inputs to guide the medical decision from healthcare professionals.

2.3. Pressure sensing

Real-time monitoring of external pressure exerted on the skin is critical for chronic wound healing, especially diabetic foot ulcers (DFUs) and pressure ulcers. Take DFUs for example, they are a major complication of diabetes, and are hard-to-heal wounds that affect millions of people (2.49 million) in the U.S [81,82], with yearly incidence ranging from 2% to 6% [83] and average annual Medicare expenditure of $29.16 billion [84]. DFUs significantly impact the quality of patients' life as they are slow to heal (78 days on average), frequently recur (40% of DFUs recur within 1 year of healing) and add additional costs. A mainstay of all DFU therapies is mechanical offloading to relieve pressure and stress on the affected foot (usually on the planar surface) [85,86], which can be accomplished through non-weight bearing (like using a walker), the use of an adaptive footwear, or the application of non-removable total contact casting [87]. However, patients' adherence to offloading recommendations has been measured as low as 2.2%, which causes significant delay in this chronic wound healing and poses a big challenge for effective treatment. Furthermore, nerve damage in DFU patients causes dramatically decreased sensation capabilities of pain and pressure, which poses additional challenges for effective offloading. Therefore, there is an urgent need to develop technologies for monitoring pressures on DFUs in real time to improve patients' adherence to offloading recommendations. Pressure ulcers are localized injuries to the skin and its underlying tissues and are usually initiated by external forces, such as pressure, shear, friction, or their combinations [88]. The prolonged pressure blocks circulation, causes the death of skin and underlying tissues, and impairs the wound healing [89]. Patients with immobility and limited activity are at risk for pressure ulcers [88,90].

The emergence of wearable pressure sensors could significantly enhance the pressure monitoring capability of skin and wound sites. Pressure sensors can be classified into four different types based on their sensing mechanism [91]: piezoresistive [92–95], capacitive [96–101], triboelectric [102,103], and piezoelectric [95,104]. Piezoresistive pressure sensors change their resistance when the applied pressure compresses the voids/pores of the patterned structure and therefore increases the pathways of electrons between two electrodes (Fig. 3A) [94]. Piezoresistive sensors are the earliest commercial type of pressure sensors due to their simple construction and operation principle [91,94]. However, piezoresistive sensors need to be powered by an external power source for continuous monitoring, which makes them more power-consuming than other types of pressure sensors [95]. A capacitive pressure sensor, consisting of a dielectric layer sanwiched by two electrodes (Fig. 3B), varies its capacitance when external pressure deforms the sandwich structure and decreases the distance between the upper and lower electrodes [98]. Capacitive sensors have several advantages including high resolution, good dynamic response, and low power consumption. However, there are still some challenges in the development of high-performance capacitive pressure sensors. For example, their sensitivity is limited by the sensing area (sensitivity rapidly declines as the sensing area decreases), and they are also defenseless against electromagnetic interference and parasitic capacitance [91,98]. Piezoelectric pressure sensors generate electric charges and change their resistance by the piezoelectric effect of materials like self-orientation ZnO nanorods and β phase polyvinylidene fluoride (PVDF) membranes [104]. Triboelectric pressure sensors are composed of a pair of negatively and positively charged materials, such as styrene butadiene rubber (SBR) and poly(dimethylsiloxane) (PDMS). With the triboelectric effect, the voltage is generated by the change of the contact surface area between negatively and positively charged materials due to the external pressure (Fig. 3C) [102]. Triboelectric and piezoelectric sensors are self-powered pressure sensors and are more sensitive to dynamic pressure signals because they can convert mechanical stimuli into electrical signals [102,104]. However, huge mechanical deformations could cause unstable pressure sensitivity of triboelectric and piezoelectric sensors, which limits their application as wearable sensors on human's joints [91,102].

Flexible pressure sensors have been developed for potential applications in wound monitoring. For example, an inductor-capacitor (LC) wireless pressure sensor was designed and fabricated to monitor the mechanical pressure on the skin wound, as shown in Fig. 3D [105]. PDMS was used as the dielectric layer of the capacitive pressure sensor, with silver conductive ink printed as spiral inductors for remote detection via a readout coil. The device was then embedded in a commercial bandage and applied to foam and pork skin respectively for evaluating its functionality (Fig. 3E). The results show the measured resonant frequency as a function of pressure in the range of 0–200 mmHg when the bandage is in contact with a pork skin and a foam, respectively. By utilizing the flexible electronic component and the passive wireless device, the smart bandage with the pressure sensing capability can potentially help manage wound conditions and improve patient comfort [105]. Despite the significant efforts in developing flexible pressure sensors, evaluation of their functionality on real patients (like those with DFUs and pressure injuries) is still less conducted, although it would offer significant guidance for the offloading and the healing of these chronic wounds. In addition, extending the measurement range of pressure sensors while maintaining a high resolution is desired to accommodate a variety of scenarios.

2.4. Strain sensing

Skin tears are traumatic wounds (sudden or unexpected injuries) resulting from shear and friction forces. Old age, impaired mobility, falls, and accidental injuries are the most prevalent risk factors of skin tears [106,107]. In addition, external shear and friction forces can also lead to delayed or interrupted healing [108]. To remove the risk factors that can cause skin tears or disrupt wound healing, wearable strain sensors are developed to track the movements and activities of the elderly and patients. Hydrogel [109–124], ionogel [125], graphene [126–131], and carbon nanomaterials [126,132–135] are the commonly used materials sensitively responding to strain changes.

The gage factor (GF), a parameter used to compare the strain sensitivity of different sensing materials, is defined by the following equations:

$$GF = \frac{\Delta R/R_0}{\varepsilon}, \varepsilon = \frac{\Delta L}{L_0}, \quad (2)$$

where R_0 is the initial resistance of the strain sensor, ΔR is the resistance change upon the applied strain (ε) [136,137]. The resistance response to the strain change is caused by structural evolution of conductive networks composed of strain-sensing materials (carbon nanotubes and graphene filled porous polydimethylsiloxane, CNT-GR/PDMS), as illustrated in Fig. 4A-C. With the increase in tensile strain, the GF value decreased from 182.5 to 45.6, then increased to 70.6 and 186.5 (Fig. 4A region I- IV). The corresponding structure evolution was shown in Fig. 4C, indicating the "point contact" (step iii), "area contact" (step iv), and breakage (step v) of the conductive network [126]. By finding a suitable material and strain range, we can improve the stretchability (applied strain) and GF value of wearable strain sensors and further enhance the performance of skin/wound monitoring. Recently, a zwitterionic skin sensor was developed to continuously monitor strain and

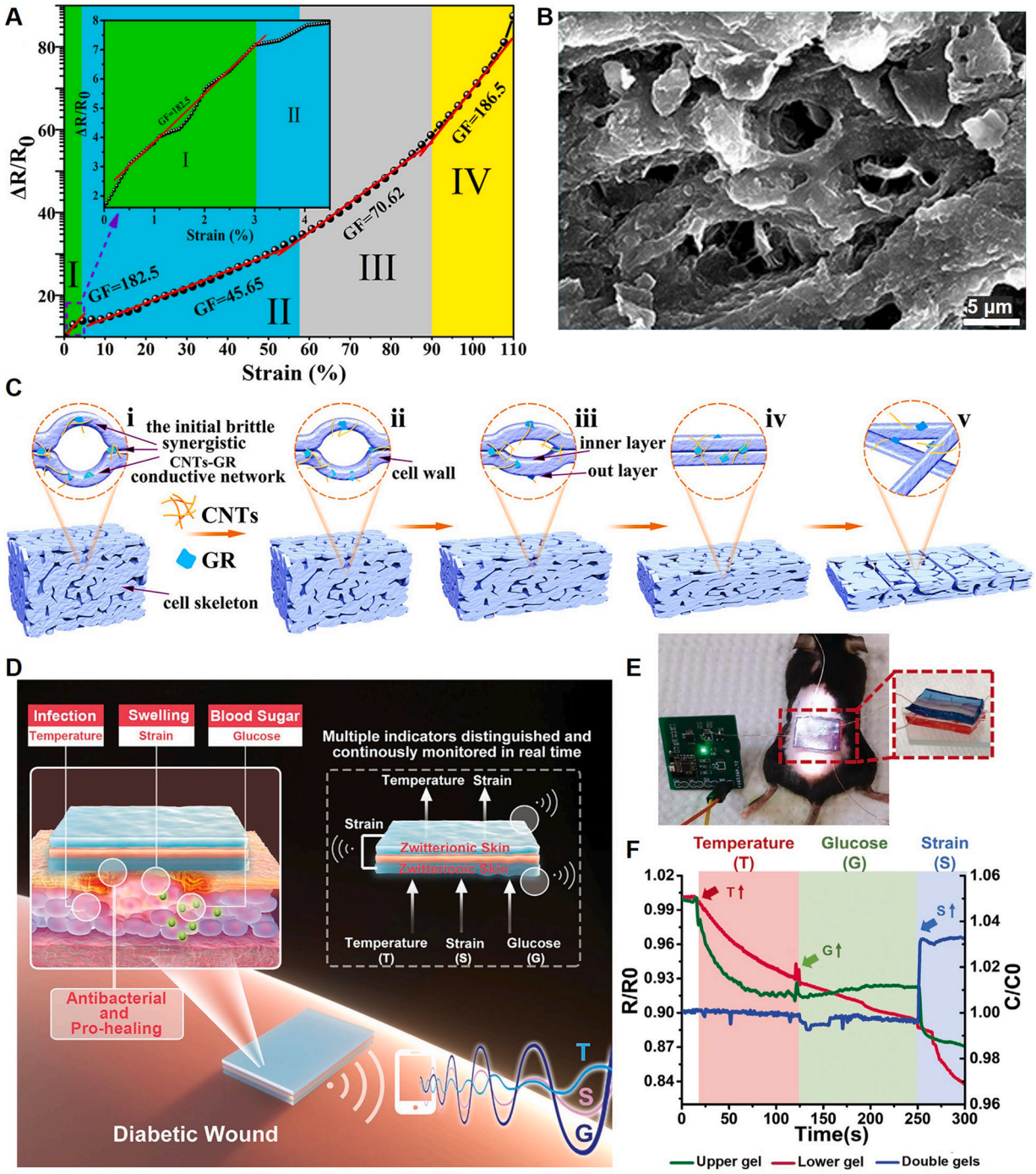

Fig. 4. (A) The sensitivity (gage factor, GF) of a strain sensor in different strain ranges [126]. (B) SEM image showing porous conductive polymer composites with synergistic CNTs-GR conductive networks [126]. (C) Schematic of structure evolution with increasing tensile strains [126]. (D) Schematic illustration of a zwitterionic skin sensor that can continuously and simultaneously monitor the strain, temperature and glucose indicators [138]. (E) Schematic photograph of real-time monitoring on a diabetic mouse wound [138]. (F) Resistance and capacitive response curves in terms of temperature (*T*), glucose concentration (*G*), and strain (*S*) that are continuously monitored and distinguished in real time [138].

other indicators like temperature and glucose to promote the healing of chronic wounds (Fig. 4D) [138]. The sandwich-structured sensor was composed of two layers of zwitterionic hydrogels with thermo-sensitive and glucose-responsive polymers and one interlayer of insulation elastomers. The strain and other indicators could be measured in real time by detecting the resistance of lower and upper layers as well as their capacitance. Furthermore, *in vivo* wound healing test was performed on diabetic mouse wounds (Fig. 4E-F), and the results demonstrated that the sensor system enabled continuous real-time monitoring of multiple indicators including strain [138].

In addition, stretchability of sensors is a significant attribute for physical sensing of wounds under moving conditions. To accomodate this need, stretchable electronic skin (E-skin) for pressure and strain detection is constructed using deep eutectic solvent (DES) gel [139], polyvinyl alcohol/cellulose nanofibril (PVA/CNF) hydrogel, and graphene oxide (GO)-doped PU nanofiber with PEDOT coating [140]. Stretchable ionic skins with strain sensing capabilities have been studied for human motion monitoring [77,139,141]. Furthermore, stretchable

multisensory systems are developed to achieve multifunctional biosignal sensing by integrating temperature, humidity, strain, and pressure sensors [142,143].

The advances in real-time monitoring of physical parameters in the wound bed have significantly facilitated the evaluation of the wound progression and wound healing. Future work of testing the sensors *in vivo*/on patients as well as integrating multiple types of sensors into one functional system is still needed to further enhance the functionality of these sensors in wound healing. In addition, developing sensors with the measurement range and resolution relevant to the wounds under a variety of scenarios (e.g., to accommodate the diversity of patients) are also desired.

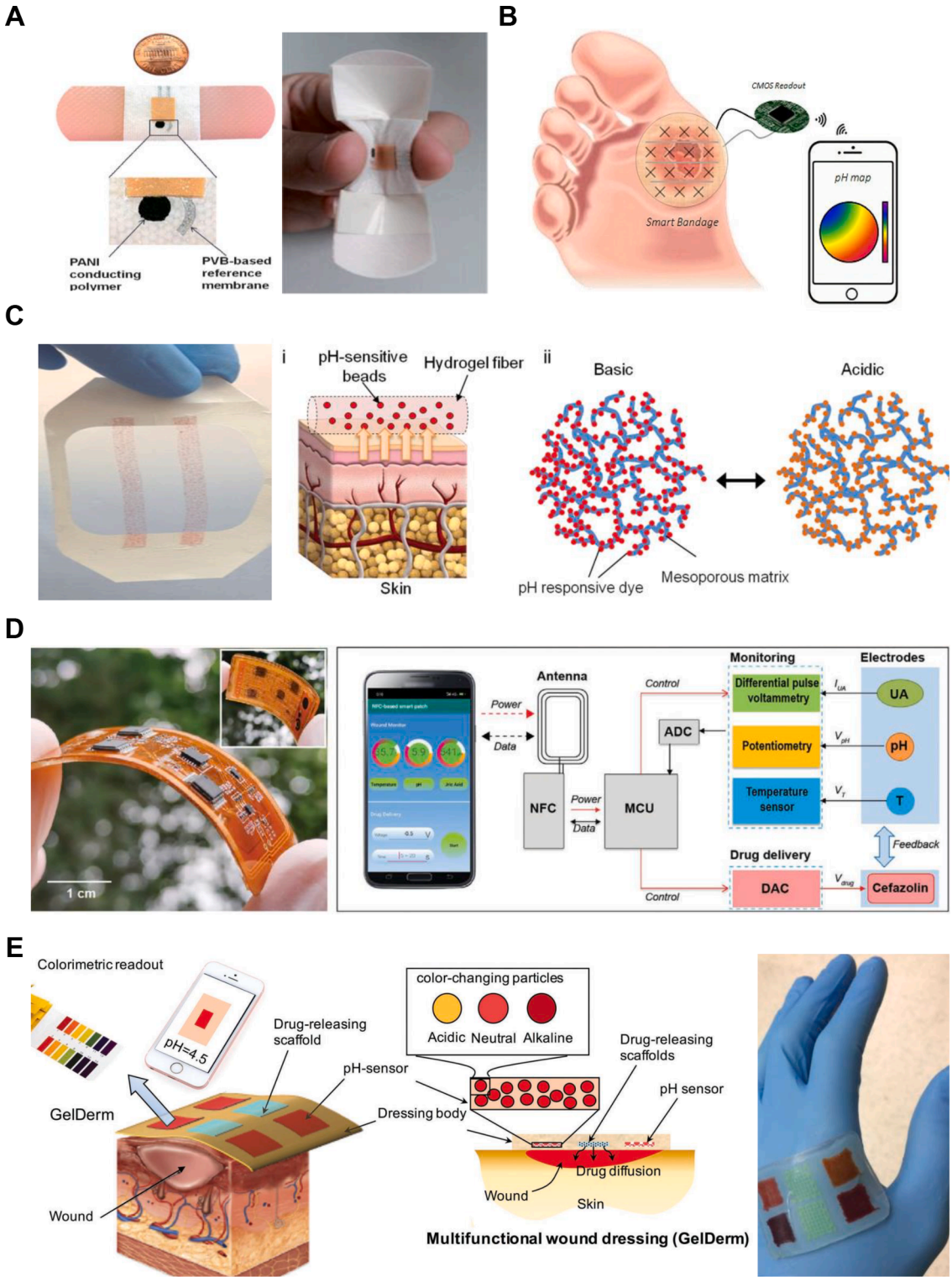

Fig. 5. Wearable pH sensors for wound monitoring. (A) A bandage-like, wearable potentiometric sensor for continuous monitoring of wound pH. [155] (B) A wireless thread-based pH sensor for monitoring the wound conditions [156]. (C) A flexible pH-responsive hydrogel fiber patch for monitoring epidermal wound conditions [157]. (D) A wearable, wireless wound dressing for online monitoring and on-demand release of antibiotics to wound site [159]. (E) A hydrogel-based multifunctional dressing for colorimetric pH sensing and controlled release of antibiotics [160].

3. Chemical sensing for wound monitoring

Among the previously mentioned wound healing stages, the chemical biomarkers of wound exudates change significantly, such as pH, cytokines and uric acid [144–146], which provide useful biochemical indications for the wound healing status and presence of infection [147, 148]. For example, the hard-to-heal wound bed exhibits an alkaline pH of 7.15 to 8.9 [149–151]. Cytokines are indicators of inflammation during the wound healing process [152]. Current methods for profiling the concentration of these important biochemical biomarkers in wound exudates often rely on laboratory testing, such as enzyme-linked immunosorbent assays (ELISAs), which are time-consuming, instrument-intensive, and requires a high level of technical skills. Recent developments in skin-integrated bioelectronics and biosensors open the door for developing wearable biochemical sensors for *in situ* wound monitoring [153,154], without the need for conventional laboratory analysis. In this section, we will focus on the recent developments of wearable biochemical sensors for monitoring pH, uric acid, and cytokines in wound exudates.

pH sensor. A chronic wound bed usually exhibits a pH of 7.15–8.9. However, it is beneficial to have an acidic environment such as pH 4–7 for wound healing since an acidic environment can support fibroblasts proliferation, improve angiogenesis and epithelialization of the wound skin, and prevent bacterial colonization for an open wound [149]. Wearable potentiometry or colorimetric pH sensors could provide important indications on the status of a wound, bacterial infections, and therapeutic management. Guinovart et al. reported a bandage-like, wearable potentiometric sensor for continuous monitoring of wound pH [155]. This wearable smart bandage uses electropolymerized polyaniline on printed carbon as a working electrode, and polyvinyl butyral polymer (PVB) modified Ag/AgCl as a reference electrode (Fig. 5A). Both working and reference electrodes were integrated onto a commercial adhesive bandage. The pH-sensitive sensor shows a Nernstian sensitivity of 58.0 $\pm$ 0.3 mV/pH, mechanical durability, high repeatability, and reproducibility. Nevertheless, the data acquisition of this wearable potentiometric sensor still relies on a laboratory electrochemical analyzer system. To fill this gap, Punjiya et al. reported a wireless thread-based pH sensor for monitoring the wound conditions [156] (Fig. 5B). The pH sensing threads were fabricated using a simple dip coating process to functionalize cotton threads with conductive carbon ink and polyaniline (PANI) nanofibers. The sensor exhibits a super-Nernstian pH sensitivity of 72 mV/pH and a fast response time ($<$ 2 min). Importantly, a customized CMOS potentiostat readout IC, an Arduino Nano, and a Bluetooth module were developed for the wireless data transmission to a smartphone user interface. This wireless data transmission enables the potential applications of the sensor beyond the conventional laboratory environments for continuous wound monitoring and timely medical interventions. Compared with potentiometric pH sensing that relies on the deprotonation of H^+ on conductive polymer PANI, colorimetric sensing, in which pH-sensitive dyes are loaded into a matrix/substrate, provides a simple and low-cost approach for pH sensing in the wound beds. For example, Tamayol et al. developed a flexible pH-responsive hydrogel fiber patch for monitoring epidermal wound conditions [157] (Fig. 5C). The patch fabrication starts with the loading of pH-responsive dyes onto mesoporous microparticles, followed by the incorporation into Na-alginate fibers using a coaxial microfluidic chip. The smartphone camera and colorimetric image analysis provide a quantitative mapping of pH. This epidermal patch can be applied as wound dressings for low-cost and continuous monitoring of pH without the need for costly instruments. The real-time monitoring of wound pH can be integrated with active drug delivery time for the closed-loop, on-demand wound monitoring and treatments [158]. The active drug delivery system was triggered through a thermo-responsive drug carrier and a miniaturized Joule heater. Similarly, Xu et al. reported a wearable, wireless wound dressing that can not only monitor temperature, pH, and uric acid on a wound site but also provide the on-demand release of antibiotics to wound site [159] (Fig. 5D). The smart wound dressings combined the near field communication module to achieve wireless monitoring purposes. Mirani et al. reported a hydrogel-based multifunctional dressing, named GelDerm, that couples the colorimetric pH sensor with controlled release of antibiotic agents [160] (Fig. 5E).

Uric acid sensor. The concentration of uric acid is strongly correlated with the wound status and infection. For example, studies have shown that the elevated concentration of uric acid in wound fluid correlates with wound severity in chronic venous leg ulcers [161]. The current wearable sensor for monitoring uric acid is usually based on the enzymatic oxidation reaction of uric acid in the presence of uricase on a working electrode. For instance, Kassal et al. pioneered the development of a wearable uric acid sensor by immobilizing the uricase on a Prussian blue modified carbon electrode [162] (Fig. 6A). The electrochemical detection of uric acid starts with the oxidation of uric acid, which generates allantoin and hydrogen peroxide. The generated hydrogen peroxide is reduced on the Prussian blue modified carbon electrode, and the reduction current is proportional to the concentration of uric acid (Fig. 6B). Fig. 6C and D show the chronoamperograms and linearity of the wearable uric acid sensor over the physiologically relevant concentration of uric acid from 100 to 800 μM. Similarly, the Bhansali group developed a wearable enzymatic uric acid sensor for continuous wound monitoring [163] (Fig. 6E). Unlike immobilizing uricase on a carbon electrode, in this study, the enzyme was entrapped into a cationic polymer matrix for enhanced stability [163] (Fig. 6F). In this study, ferrocene carboxylic acid is used as a redox electron shuttle to interface the graphite electrode and uricase (Fig. 6F). The monitoring of uric acid is based on the redox reaction of ferrocene carboxylic acid on the enzymatic electrode (Fig. 6G). Importantly, the uricase entrapped electrode shows a superior response towards the detection of uric acid mainly due to the increased diffusion of analytes toward the working electrode (Fig. 6H). Nevertheless, these existing studies still use enzyme, uricase, and multiple steps surface functionalization. A recent study demonstrates a novel wearable uric acid sensor for sweat monitoring based on the direct oxidation of uric acid on laser-induced porous graphene surfaces [164], which could be adapted for the wound healing applications.

Cytokine sensor. Although the biosensor technology is undergoing an exponential development, flexible and wearable cytokine biosensors that are capable of monitoring the wound healing process are limited since most wearable sensors for wound monitoring are pH, temperature, uric acid, and oxygen sensors [148]. Kim et al. reported a stretchable electrochemical biosensor to detect tumor necrosis factor-α (TNF-α) in artificial wound exudate (Fig. 7A) [165]. In this study, the TNF-α antibody was used as a sensor receptor and differential pulse voltammetry was used for the electrochemical signal acquisition. This stretchable electrochemical sensor achieves the detection level down to 100 fM in PBS solution (Fig. 7B). It should be noted that gold working and counter electrodes and Ag/AgCl reference electrode are prepared on a stretchable micro-patterned silicone elastomer substrate (Fig. 7A). Such a stretchable sensor enables the robust and stable sensing performance even after 1000 cycles of stretching and 30% elongation (Fig. 7B), suggesting the potential applications to interface with dynamic human skin. Nevertheless, this stretchable immunosensor can only measure one type of cytokine, and the multiplex monitoring is lacking. Recently, Gao et al. pioneered the development of a flexible, wearable multiplexed immunosensor, termed VeCare, for the *in-situ* monitoring of wounds at the point of care (Fig. 7C–F) [166]. The VeCare includes three key components as follows (Fig. 7C): (1) A Phrynosoma cornutum skin-inspired passive microfluidic collection system, thereby enabling the wound exudates to be collected and guided into a set of sensor areas, (2) An array of sensors that can analyze the inflammatory biomarkers (TNF-α, interleukin-6, interleukin-8, and transforming growth factor-β1), staphylococcus aureus (S. aureus, a biomarker for microbial burden on wounds), temperature and pH, and (3) A wireless data

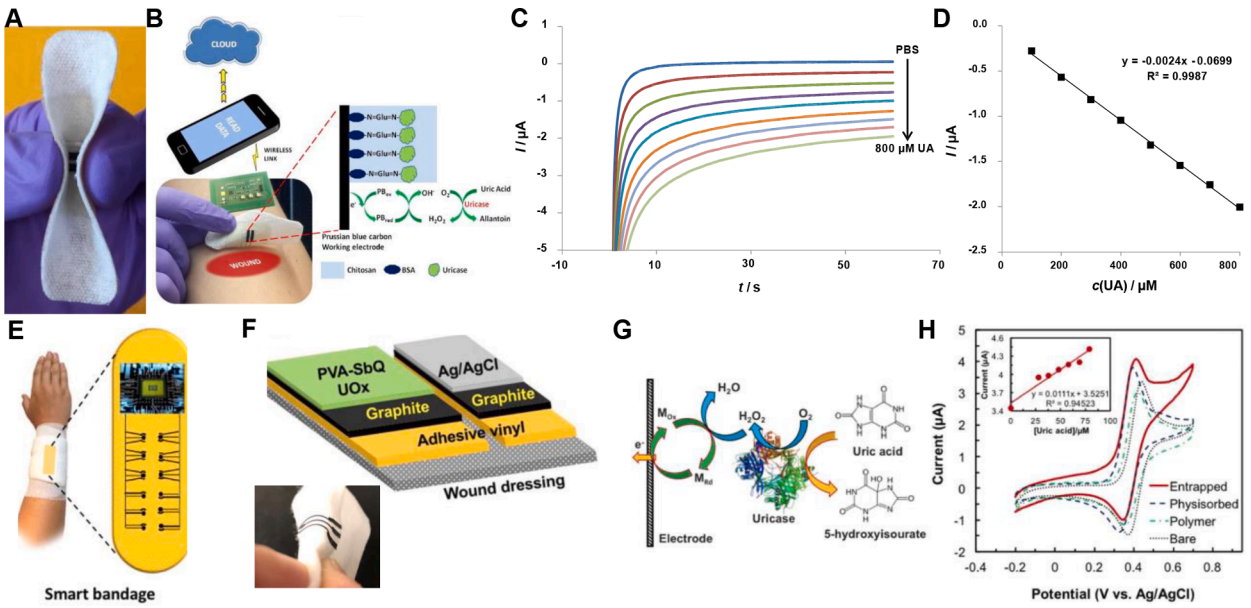

Fig. 6. Wearable uric acid sensors for wound monitoring. (A) Optical image of a wearable enzymatic uric acid sensor. (B) Working principle of the wearable uric acid sensor. (C) The chronoamperograms and (D) linearity of the wearable uric acid sensor over the physiologically relevant concentration from 100 to 800 μM [162]. (E) A wearable enzymatic uric acid sensor for continuous wound monitoring. (F) Schematics for the surface functionalization of working and reference electrodes. (G) Working principle of the enzymatic uric acid sensor. (H) The uricase entrapped electrode shows a superior response towards the detection of uric acid [163].

transmission system based on a low-power Bluetooth system to achieve real-time data collection, visualization, and clinical management. The measurement of inflammatory biomarkers is based on the aptamer-electrochemical method. A nanocomposite based on electrochemically exfoliated graphene-gold nanoparticles (AuNPs-GP) was functionalized on a gold working electrode due to its high conductivity, enhanced electron mobility, and superior electrochemical performance. The working electrode was then functionalized with methylene blue (MB, an electrochemical tag) labeled aptamers, which have high selectivity towards a targeted cytokine or bacteria. The electron transfer between the working electrode and redox-active MB was acquired by using square wave voltammetry (SWV). In the absence of a target (such as cytokine), the aptamer is folded, which results in a high electron transfer rate. In the presence of a targeted analyte, in contrast, the conformation change of aptamer modulates the electron transfer between MB and the working electrode and decreases the current. The background-subtracted peak current decreased with the increase of the concentration of measured cytokines. The VeCare shows good sensitivity, selectivity, minimal interference, and high reproducibility towards the measurement of TNF-α, interleukin-6, interleukin-8, transforming growth factor-β1, and S. aureus within the physiologically relevant range in wound fluids (Fig. 7D). The VeCare indicated a good biocompatibility in a mice wound model and a clinical application for monitoring wound exudates for patients with venous ulcers (Fig. 7E–F). Nevertheless, the long-term and continuous monitoring of cytokines is still challenging. To tackle this challenge, future work should focus on the following aspects: (1) the development of reversible bioreceptor of the sensor, thereby enabling the continuous monitoring, (2) improving the sensitivity and selectivity due to the ultralow concentrations of cytokines in wound exudates and their diverse chemical environment, and (3) developing biofouling resistance coatings for long-term monitoring in complex wound beds.

4. Wound management

As described previously, wound healing is based on the sequence of biological events that if not occur effectively, tissue repair can be halted. Chronic wounds typically suffer from multiple pathologies, and most of the times, multiple therapeutics are needed to eliminate pathologies or encourage physiological processes. To this end, the wound healing therapies have been focused on the paradigm of "what therapeutics" and "when to be delivered". Many researchers have developed dressings that allow the local delivery of therapeutics to the wound bed. These therapeutics could range from a single protein or small molecule to cells and blood derived products [167].

An optimal drug delivery system should release specific therapeutic agents corresponding to the spatiotemporal physiological requirements throughout wound healing stages. Drug delivery systems can be classified into passive, active, and smart systems, either incorporating smart materials reacting to wound biomarkers or integrated sensing/delivery systems [25]. Passive approaches utilize a continuous release of drugs from the wound dressing, controlled by the inherent release kinetic of the specific drug from the dressing network. On the other hand, active systems employ an external stimulus (e.g., temperature, electrical signal, light, etc.) for on-demand induction of the release. Finally, smart systems detect the need for a specific drug based on various biomarkers in the wound environment and trigger the release of the drugs when required [168].

A passive drug delivery relies on the diffusion of the therapeutic factor through the drug carrier to reach the wound bed. Various organic (such as liposomes and hydrogels) and inorganic (such as ceramics, carbon nanotubes, and metallic particles) drug carriers have been developed for drug delivery in wound healing applications [3,169–172]. The main goal of passive drug delivery systems is to control the release kinetics based on carrier pore size, hydrophilicity, degradability, and its relative electrostatic charge compared to the drug. Generally, a sustained release of the therapeutic is preferred over a burst release, due to reduced local availability of the drug throughout the required period of time when it is applied with a burst release [173]. Polyesters, hydrogels, and liposomes are the most widely used materials implemented as drug carriers in wound healing applications [174–178]. Nanoparticles can be utilized to better penetrate the wound bed and offer larger surface area to volume ratio in comparison to their microsized counterparts. There are several comprehensive review papers discussing the advantages and shortcomings of passive drug delivery systems and will not be covered here [179–181].

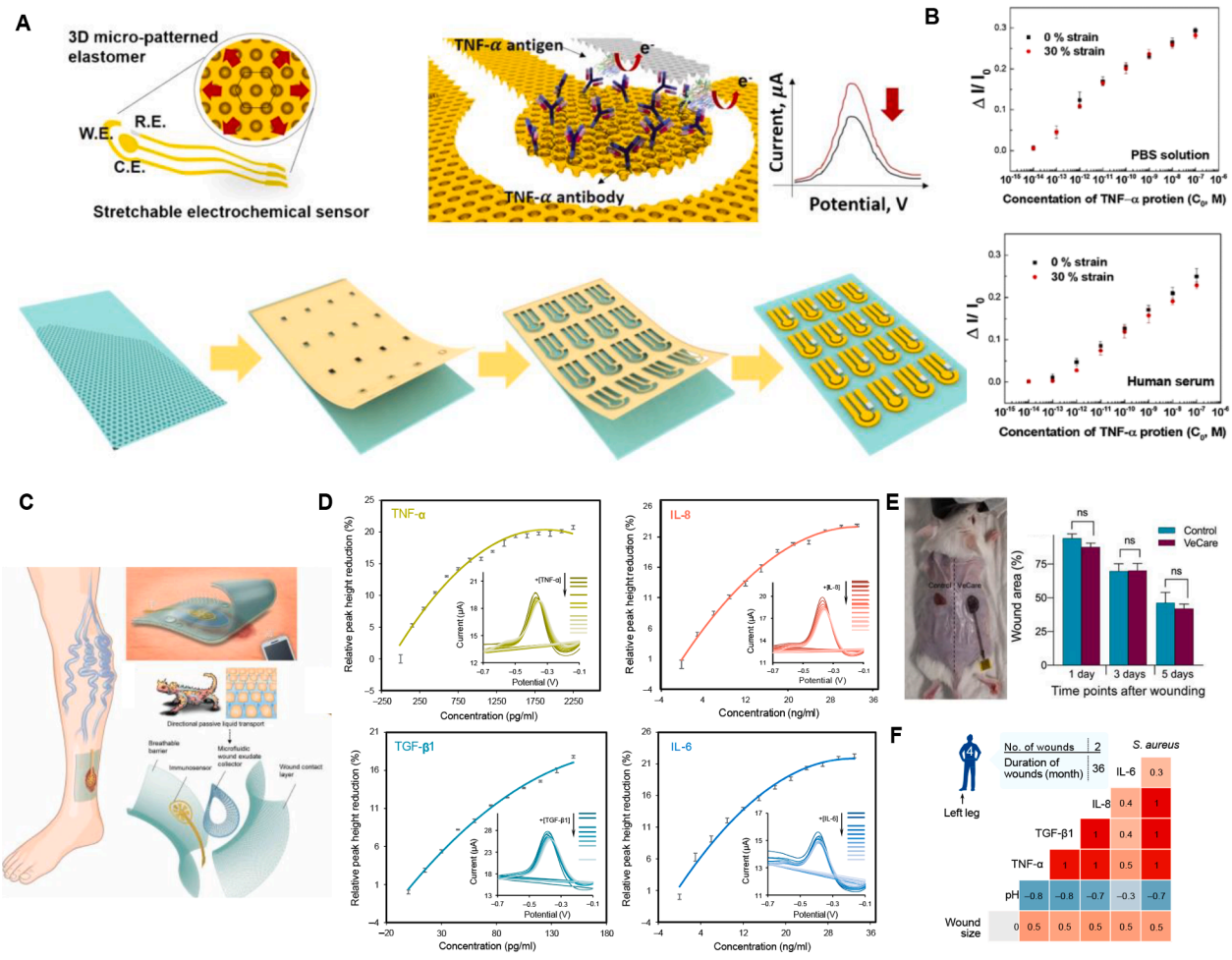

Fig. 7. Wearable cytokine sensors for wound monitoring. (A) Schematic illustration of the working principle and fabrication process of a stretchable electrochemical biosensor to detect TNF-α in artificial wound exudates. (B) The calibration curves of the electrochemical biosensor to detect TNF-α in PBS solution and human serum under various strains [165]. (C) Schematic illustration of a wearable multiplexed immunosensor, termed VeCare, for the *in-situ* monitoring of wound at the point of care. (D) The calibration curves of VeCare towards the measurement of various biomarkers within the physiologically relevant range in wound fluids. (E) Biocompatibility study of VeCare in mouse wound model. (F) A clinical application example for monitoring wound exudates for patients with the venous ulcer [166].

Recently, there have been a few studies that demonstrated the importance of the point of delivery and spatial distribution of therapeutics on wound healing [182,183]. While skin injuries are accessible and in the first glance, topical delivery of therapeutics should ensure their delivery to the target cells, chronic wounds are covered by eschar, occasionally exude, and their environment is rich with proinflammatory cytokines and enzymes. These characteristics can potentially lower the local availability and effectiveness of therapeutics [184].

In this section, first we will review the devices that allow delivery of drugs in an on-demand fashion. We will also discuss strategies for improving the spatial distribution of therapeutics within the wound bed. After that, we will highlight other types of stimulations that can improve wound healing and will discuss some of the advanced dressings that locally applied these stimulations.

4.1. *Systems for on-demand drug delivery*

There is a significant push towards the personalization of wound care products and strategies. To achieve this goal, systems that can deliver therapeutics on demand or actively are needed [25,185]. The efforts in this area have been divided into two approaches: (1) strategies that utilize smart materials that respond to the changes in the environmental conditions within the wound site and release therapeutics to regulate the environment [186,187]; (2) systems that utilize external stimulations for initiating and maintaining the release of therapeutics. In this section, we will focus on the second approach and readers are referred to recent reviews on smart materials for wound healing applications [188,189].

External stimulations that are selected for activating the drug release should be safe, specific, without side effects, and different from signals generated by host body. The stimulation commonly used by researchers include temperature change, electric field, and light [3,25].

Thermo-responsive drug delivery systems have been widely utilized for on-demand delivery of therapeutics. In these systems, thermo-responsive polymers such as poly(N-isopropylacrylamide) (PNIPAm), chitosan, and Pluronic are used as drug carriers and are interfaces with heaters that locally elevate the temperature [190,191]. In one notable study [36], a thermo-responsive textile dressing was engineered in which every single thread on the patch was a heater coated by a layer of alginate hydrogel carrying PNIPAm-PEG copolymers loaded with a specific drug (Fig. 8A). Different drugs were loaded on different threads and each thread could be stimulated separately. Furthermore, the dosing of the drugs could be controlled by the rate and number of activated threads (Fig. 8B). To demonstrate the potential of this system, an animal study was performed by loading a vascular endothelial growth factor (VEGF) in the dressing. Interestingly, results showed an enhancement of granulation and wound closure in diabetic animals (Fig. 8C,D). However, the limitation of thermo-responsive drug delivery systems is that the target temperature should not be too high to irritate the tissue or

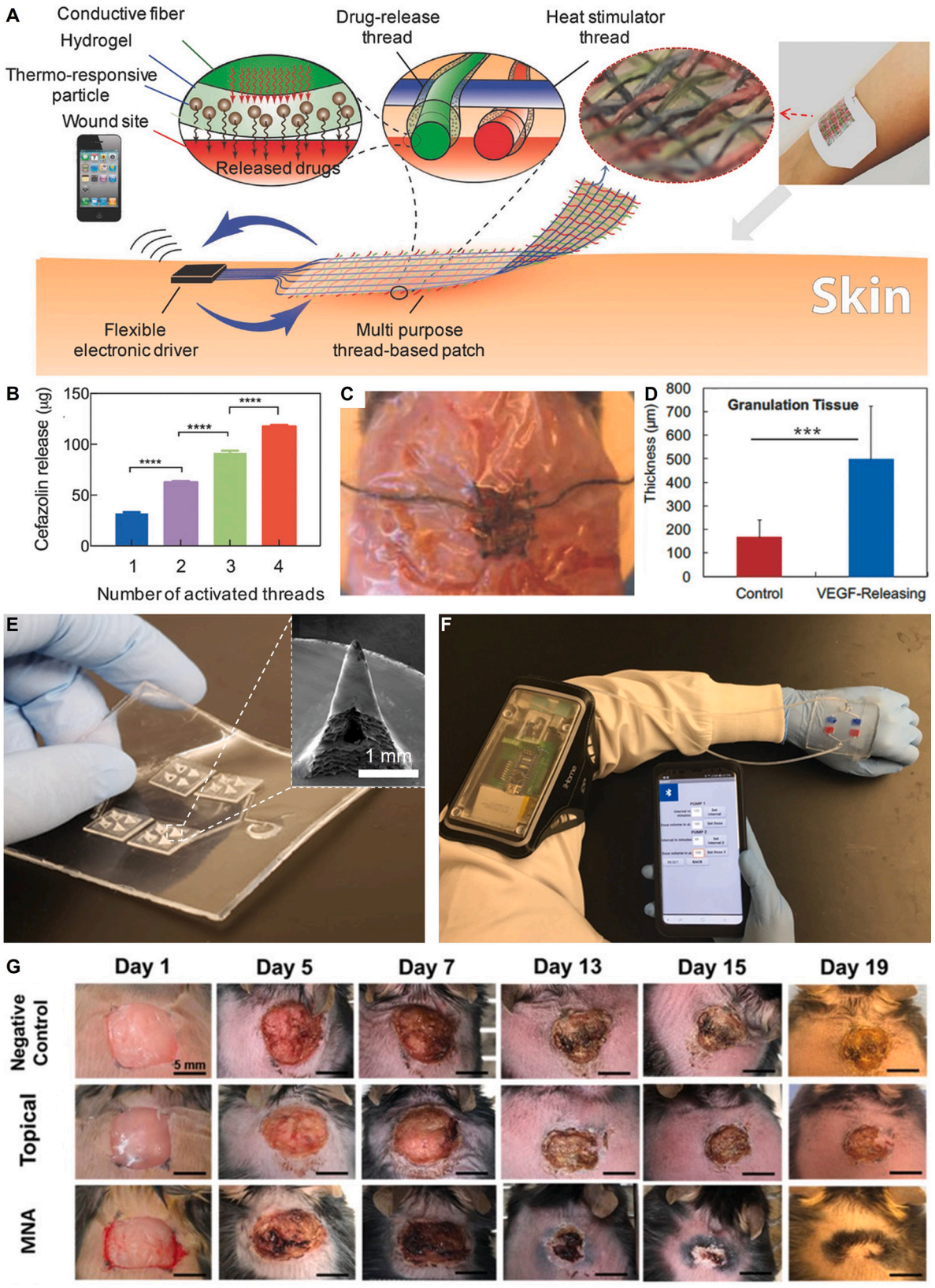

Fig. 8. Examples of systems for on-demand delivery of drugs for wound healing application. (A) Schematic of a textile dressing where different threads in the dressing were loaded with a dose of a specific drug and could be triggered independent of other threads in the dressings. (B) Effect of the number of triggered threads on the quantity of the released drugs. (C) The application of a typical dressing on diabetic mice with full thickness skin injuries. (D) The comparison of the thickness of granulation tissue 10 days post-surgery [36]. (E,F) Two-module dressing with integrated microneedle arrays benefiting from micropumps for the delivery of a precise volume of drugs. (G) The delivery of VEGF as an angiogenic factor for the treatment of diabetic wounds clearly showed the benefit of microneedle mediated drug delivery in inducing tissue regeneration [183].

deactivate the drugs. On the other hand, the selection of the critical temperature close to the body temperature carries the risk of unwanted drug release in warm climates.

Another stimulus used for active drug delivery in wound healing applications is the electrical signal. In one example, researchers engineered a dressing with electrodes coated by layers of hydrogel carrying pH responsive drug carriers [185]. The application of electrical current between the electrodes was shown to locally change the pH at the vicinity of the electrodes, triggering the release of the drug. The shortcoming of this strategy is that pH in the wound environment can change over time and therefore the drug release could be affected by that, negatively impacting the programmed release kinetics. Electrical fields can also be directly used for the delivery of therapeutics to the wound bed. If charged molecules or drug carriers are used, then by application of an electrical field, therapeutics can be delivered intradermally [192, 193]. This strategy has shown to be effective in the delivery of genes and drugs to the wound bed and consequently improving wound healing.

While the utilization of different external stimulations could assist the delivery of therapeutics to the wound beds, these strategies always carry the risk of unwanted drug release and suffer from the need for bulky equipment and complex designs, which complicate the regulatory process. One of the most robust strategies for precise temporal control over the drug release is the delivery of liquids via micropumps. In a notable example, a two-module dressing was engineered consisting of an electronic module containing reservoirs, micropumps, control and wireless communication units, as well as a dressing module with integrated 3D printed hollow microneedles to deliver drugs into the wound bed [183]. Multiple drugs could be loaded into the electronic module and then pumped toward the dressing module to be delivered to wounds (Fig. 8E,F). The delivery of therapeutics could be precisely programmed and controlled, independent of environmental conditions. To better control the spatial distribution of therapeutics and enhance the penetration of the drugs into the wound bed, microneedle arrays were integrated to the dressing module. During the animal studies, the delivery of VEGF via microneedles showed a significant enhancement in diabetic wound healing in comparison to their delivery topically (Fig. 8G). However, the shortcoming of this strategy is that it works with drug solutions and therefore the delivery of hydrophobic molecules could be challenging.

Active drug delivery systems can be integrated with biosensors to engineer smart wound dressings. One of the goals of engineering smart wound care products is to reduce the need for visits to healthcare facilities and decrease the time between the occurrence of an abnormality in wound healing and administration of therapeutics [25,168]. In this

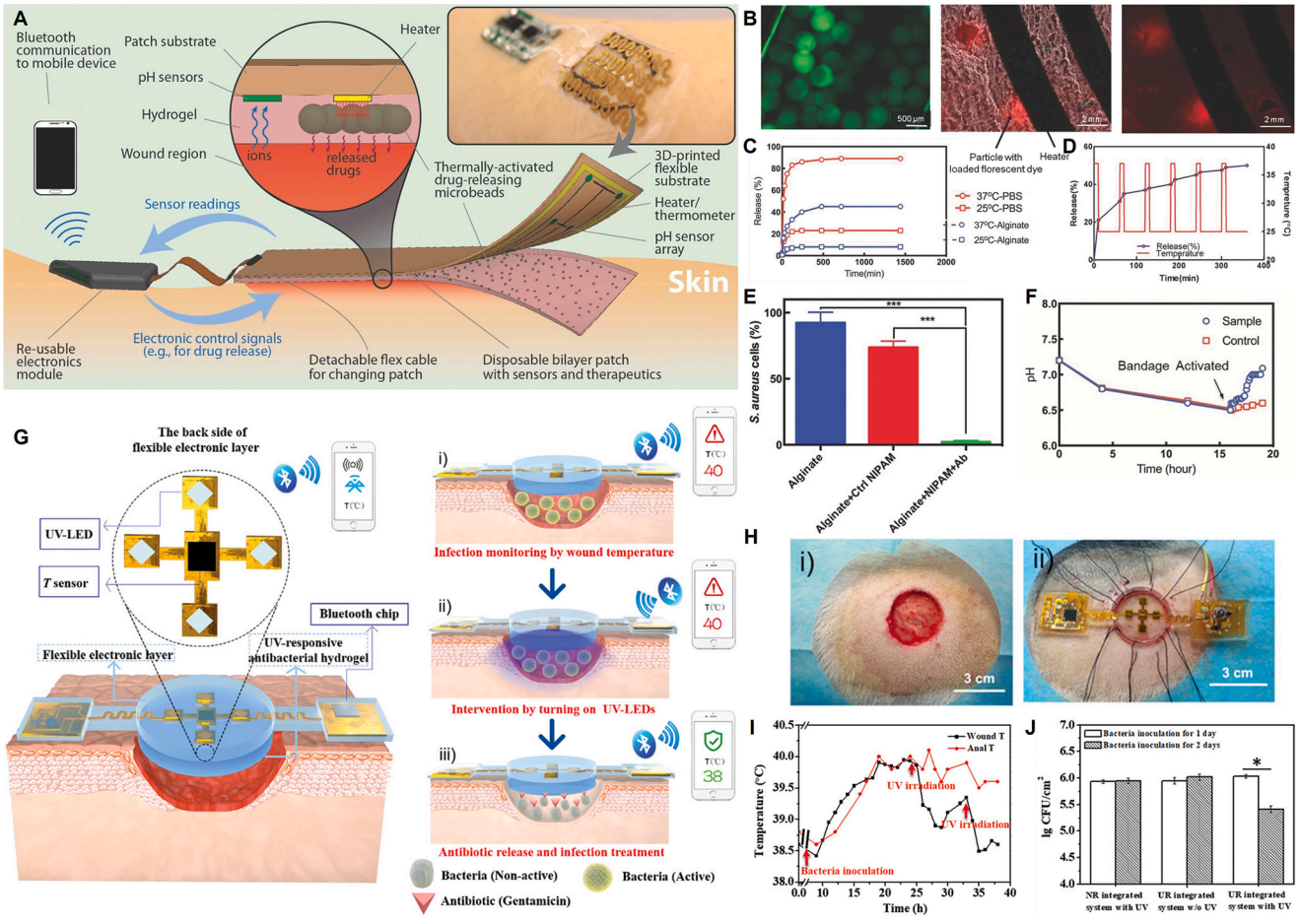

Fig. 9. Smart systems with integrated sensors for on-demand drug delivery. (A-F) A pH responsive smart dressing for treatment of infected wounds. (A) The working mechanism of the device. The device consisted of a two-layer patch, in which the top layer is embedding heating elements, while the bottom layer is a thermo-responsive hydrogel and a flexible pH sensing array. The platform also has a separate wireless communication module. (B) The release of florescent drugs from thermo-responsive drug carriers upon thermal stimulation. (C) Drug release profile from microcarriers encapsulated in PBS or alginate matrix. (D) Quantitative results of thermally released drugs from the hydrogel [194]. (E,F) Bandage activation upon pH change and decreased viability of bacteria *in vitro*. (G–J) A temperature responsive smart dressings for treatment of infection in wounds. (G) The operation mechanism of the platform where a flexible temperature sensor detects infection induced hyperthermia and the integrated LED triggers antibiotic release. (H) The *in vivo* application of the integrated platform in an animal model of full thickness injury. (I) The plot of wound temperature measured by the integrated sensor (black) compared to an analogue thermometer (red). (J) Statistical analysis of the bacterial load treated with different conditions showing the effectiveness of the platform in lowering the density of bacteria [195].

case, automated devices that can process the wound conditions and decide on the need for the delivery of therapeutics could achieve this goal. In a pioneering study, a smart and automated dressing was engineered in which the dressing was equipped with pH sensors for the monitoring of the wound bed [194]. The changes in the pH could indicate the colonization of wound with pathogens. The platform had an integrated hydrogel layer carrying antibiotic loaded thermo-responsive drug carriers. Upon changes of the pH at the wound environment, the dressing could trigger an integrated heater starting the release of antibiotics (Fig. 9A,B). The release of antibiotics could be adjusted by controlling the patch temperature (Fig. 9C,D). The released antibiotics were potent, and the platform was shown to be effective in eradication of bacteria in a biomimetic *in vitro* model (Fig. 9E,F).

In another study, a flexible two-layer smart bandage was designed for on-demand treatment of infected wounds [195]. In the wound dressing, the top layer contained a temperature sensor and embedded UV lights, while the lower layer interfacing with the wound environment was a PEG-based hydrogel supplemented with gentamicin, an antibacterial drug (Fig. 9G). The PEG-based hydrogel was designed to be responsive to UV light, cleaving gentamicin through UV exposure. Upon the occurrence of infection, an inflammation state would happen, which could increase the temperature of the wound environment. The temperature was detected by the sensor through an integrated wireless system, communicating to a cell phone device, programmed for decision making. Therefore, excessive heat as a result of infection triggered a signal sent from the cell phone to the device for the activation of UV lights and the release of antibiotics. Animal studies demonstrated successful activation of the system upon infection and treatment of infected wound (Fig. 9H–J). However, the limitation of this temperature-responsive system as described previously is unexpected release of antibiotic when the patient is suffering from fever, or in warm weather.

Overall, while the use of automated dressings seems exciting, it should be noted that automated dressings mostly are needed for responding to severe complications such as infection or excessive inflammation. Any of these issues can easily be treated at the beginning, but if left untreated, it could quickly lead to life-threatening complications, specifically for high-risk patients, for example, those suffering from diabetics. However, the successful translation of these technologies requires the monitoring of specific markers. In the case of infection, the detection of pathogen strain is needed, which can further complicate the translation of such systems.

4.2. Non-drug stimulations for wound healing

The tissue, infection, moisture, and edge of wound management (TIME) has been followed as a standard-of-care [196,197]. As a result, the research and clinical efforts have been focused on the removal of necrotic tissue, eliminating bacterial load, modulating the tissue moisture level, draining excessive exudate, and encouraging tissue ingrowth. The goal of these efforts is focused on effectively treating an existing episode of skin injury and preventing its recurrence in the future. Pain management is also an important area that affects the quality of life and the adherence of the patients to therapies [198–202].

Engineering tools have been utilized to develop several tools for better management of wounds. Negative wound therapy (NPWT) systems are one class of engineering tools successfully used in clinical wound care [203,204]. In these strategies, the wound will be covered by a chamber mostly filled with a foam or porous structure and negative pressure will be applied. The negative pressure reduces the compression on the wound edge [205]. In addition, these systems are known to modulate the environment through inducing macro and micro deformations to the wound surface, helping wound debridement and extraction of biofilm and wound exudates rich with pro-inflammatory cytokines, and creating a gradient of angiogenic factors such as VEGF [206]. However, one limitation of such systems is their inability to deliver therapeutics and growth factors to the wound bed while under negative pressure. Also, it is important that tissue strain is monitored to ensure it is not excessive, because excessive strain could have negative consequences on both the tissue and effective drug delivery from any potential advanced wound dressing.

Oxygen is an important factor in wound healing and researchers have explored strategies for enhancing the level of tissue oxygenation [3]. Oxygen is essential for the metabolic activity of cells and their growth [207]. The traditional strategy of using hyperbaric oxygen therapy (HBOT) has shown some improvement in wound healing, but also carries the risk of oxygen poisoning and lung injuries [208]. An alternative strategy has been to use topical oxygen therapy (TOT) in which a chamber is formed around the wound and filled with air containing a higher concentration of oxygen [209]. To improve the oxygen penetration, perfluorocarbon emulsions have been utilized to improve the oxygen penetration into the tissue [210]. However, these strategies are expensive, challenging to apply, and carry the risk of post-exposure complications. Another strategy has been to use oxygen-generating materials in engineering dressings. In one example, a fluidic based-flexible dressing was engineered in which H_2O_2 was flown over a hydrophobic porous substrate coated with catalyst-sputtered islands (Fig. 10A,B) [211]. Catalysts facilitated the production of O_2 directly at the wound interface. In another study, the team engineered a platform capable of both oxygen sensing and generating. Therefore, by monitoring the level of oxygen at the wound interface, the dressing could generate oxygen on demand to prevent hypoxia (Fig. 10C–E) [212]. However, in the animal studies, the platform did not show significant improvement in the healing of acute wounds [212].

Improving wound healing through encouraging cell ingrowth has been a center stone of research efforts. People have utilized different types of stimulation to encourage a faster wound closure rate [25]. In one example, a flexible enzymatic fuel cell was utilized to generate electrical current towards the center of the wound and to direct the ingrowth of epithelial cells (Fig. 11A) [213]. The results showed a faster wound closure in the animal studies. In another study, an alternating discrete electric field was applied by wearable devices (Fig. 11B,C) [214]. This strategy showed a wound closure over 3 days in comparison to the control groups which took about 12 days (Fig. 11D, E). In another study, a stretchable and flexible triboelectric patch was formed to electrically stimulate the wound bed (Fig. 11F) [215]. Upon the application of the platform on animal models, it was observed that wound healing was expedited by the periodic contact and separation between the layers (Fig. 11G, H). Piezoelectric materials have also been used as nanogenerators for applying electrical stimulation to wounds and enhancing wound [216].

Biomechanical cues can significantly affect the growth and migration of cells [217]. Therefore, applying instructive biomechanical cues have been explored for improving wound healing. One of the most common strategies for stimulating cells to contribute to wound healing is controlled application of ultrasonic waves [218]. In one example, a wearable device capable of applying low frequency (20–100 kHz) ultrasonic waves were used as a dressing [219]. The platform was applied to human subjects suffering from DFUs. The groups receiving the ultrasonic stimulation showed a significant improvement in the wound healing rate.

The delivery of different stimulations to wounds have shown a great promise in inducing wound healing. However, most of the studies have focused on the application of one type of stimulation. The potential synergy between biochemical stimulations and other physical stimulations has not been well explored and could further augment the outcome of the therapy.

5. Integration with other advanced technologies for wound healing and management

Wearable biosensors provide a unique opportunity to assess wound

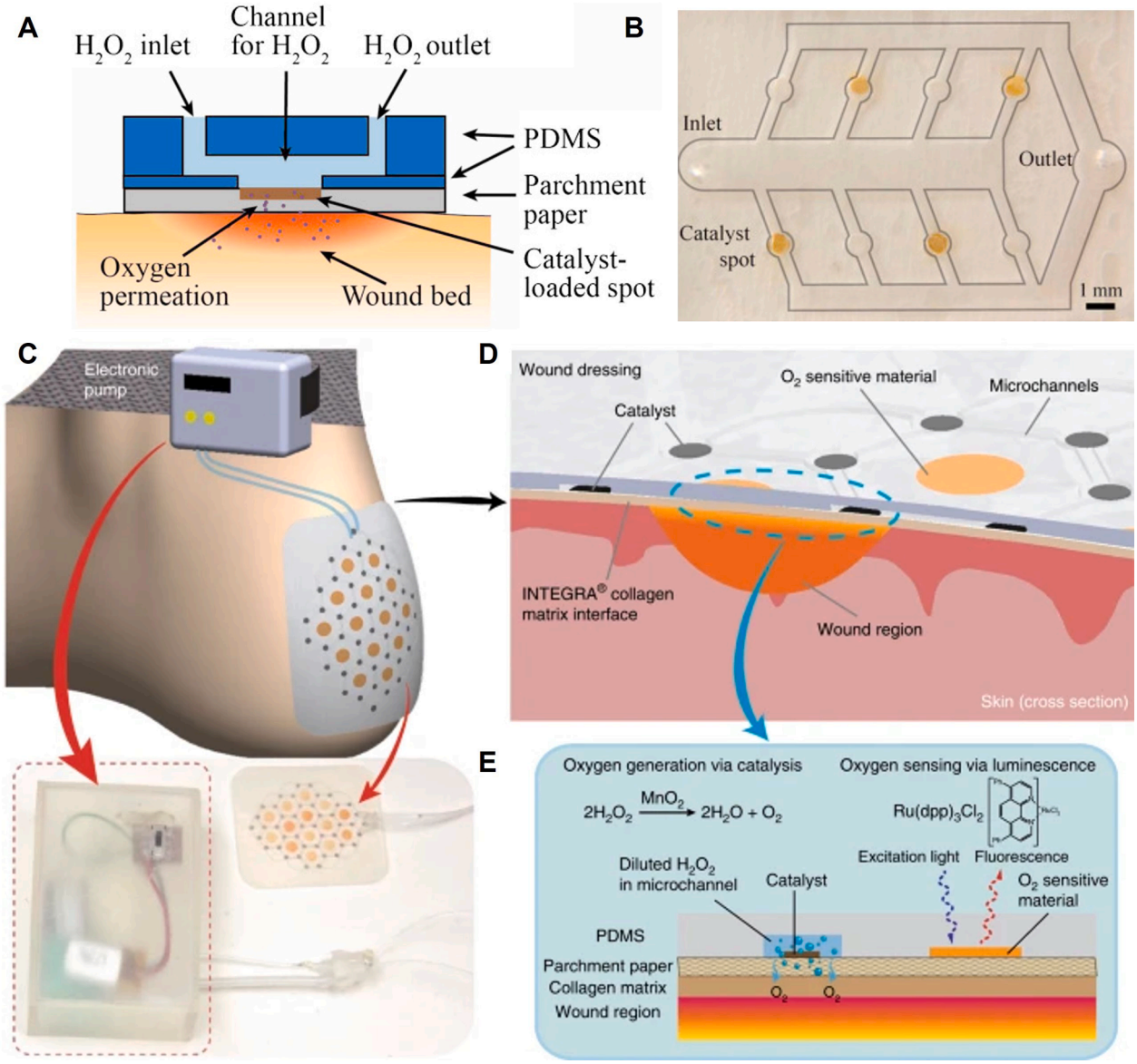

Fig. 10. Oxygen delivery dressings for wound healing applications. (A) Schematic of the platform operation in utilizing H_2O_2 for oxygen generation. (B) A representative photograph of the platform with 4 spots functionalized with catalysts [211]. (C) Schematic of a dressing with integrated oxygen sensors and generators for treatment of foot ulcers. (D) The cross-section of the sensing and generation modules at the wound interface. (E) The mechanisms of oxygen sensing and generation within the dressing [212].

healing progress in a continuous, real-time, and non-intrusive manner [220]. Based on various types of biosensors, sensing data in the form of physiological parameters such as body temperature, pressure, and skin moisture level, and chemical parameters such as pH value and inflammation biomarkers can be massively collected from different users [221]. Despite the significant advances in biosensors that have been made in the past decade, most of the sensing data often contain irregular signal noise and some of them may exhibit poor stability since these biosensors rely on antibodies or aptamers as bioreceptors [222]. Consequently, there is a great need to leverage advanced analytic techniques, i.e., machine learning and deep learning, to analyze the data collected based on biosensors to better assess and manage the wound healing process.

An effective data-driven wound healing assessment and management system will consist of four major components, i.e., data collection, data preprocessing, feature extraction or representation, and output (based on different assessment tasks) as shown in Fig. 12. For data collection, various physiological parameters and chemical parameters will be collected via different types of biosensors; for data preprocessing, missing values will be handled, noise, redundancy and correlation will be assessed, and normalization will be performed if necessary [223]. In this section, we mainly focus on discussing existing machine learning techniques for feature extraction/representation of biosensor data and addressing some practical problems (e.g., classification, prediction, and clustering) for wound healing as shown in Fig. 13.

5.1. *Feature extraction/representation*

Although raw sensing data that are continuously recorded can be directly used as the input for wound healing assessment systems [222, 224], they often contain noise and thus could heavily affect the performance of these systems. To resolve this issue, various feature extraction methods, e.g., principal component analysis (PCA) [225] or linear discriminant analysis (LDA) [226], can be applied. Specifically, PCA aims to reduce the dimension of input by preserving the variance of the input sensing data while LDA can maximize the inter-class distance

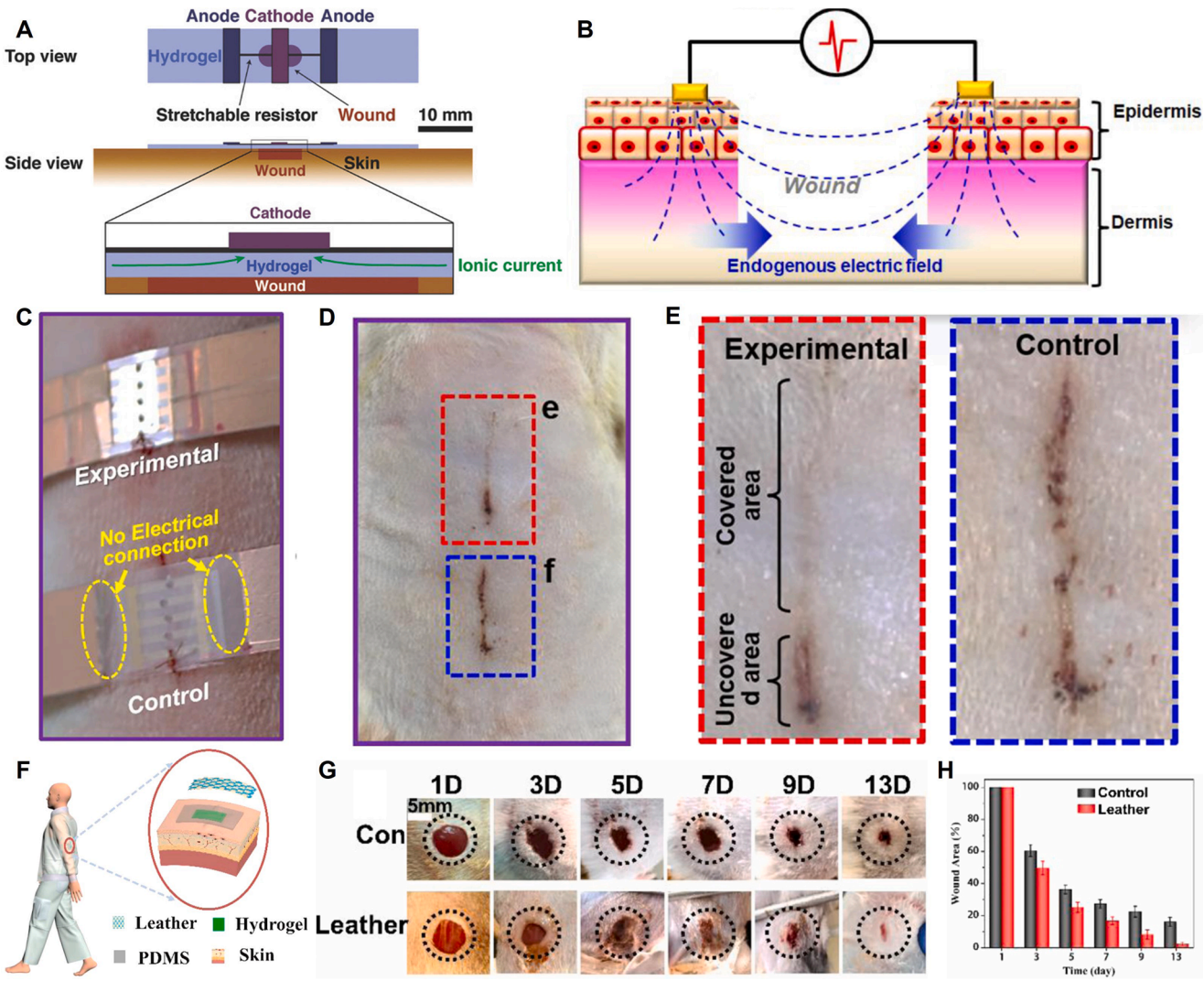

Fig. 11. Various types of electrical stimulation of wounds. (A) Schematic of the operation of the enzymatic biofuel cell (EBFC) for improving wound healing [213]. (B) The mechanism of operation of electrodes applying alternating electrical fields to expedite wound healing. (C) Representative image of dressings with connected electrodes (experimental group) and disconnected electrodes (control group). (D,E) Photographs comparing wound closure between the experimental and control groups [214]. (F) Schematic of the architecture of the dressing for triboelectric stimulation of the wound. (G,H) The comparison of the wound closure rate in response to the dressing with triboelectric stimulation and control group [215].

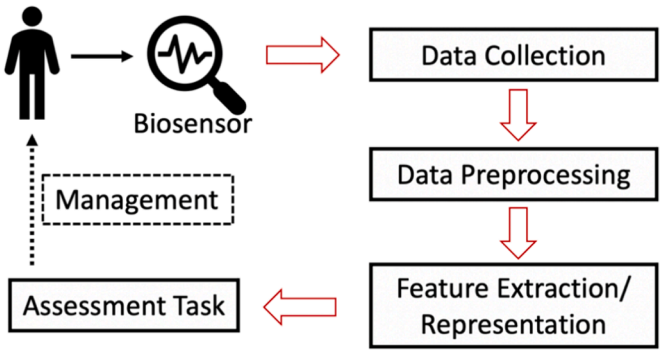

Fig. 12. Machine learning pipeline for wound healing assessment and management.

and minimize the intra-class distance when label information is available. Moreover, since the raw sensing data are usually time series, traditional techniques such as discrete Fourier transform (DCT) [227, 228], discrete wavelet transform (DWT) [229], and piecewise aggregate approximation (PAA) [230] can be used to obtain a compact representation of the raw time series data in order to facilitate the underlying applications.

Traditional feature extraction approaches, however, may not be able to capture the potential complex non-linear relationships among the sensing data for specific tasks. Consequently, Recurrent neural networks (RNNs) [231, 232], a type of deep neural network specially designed for sequence modeling, have received a great amount of attention for time series sensing data representation due to their flexibility in capturing nonlinear relationships. Traditional RNNs, however, suffer from the problem of vanishing gradients [233] and thus have difficulty capturing long-term dependencies. Recently, long short-term memory units (LSTM) [234] and the gated recurrent unit (GRU) [235] have overcome this limitation and achieved great success in various applications, e.g., time series classification, forecasting, and anomaly detection. Meanwhile, convolutional neural networks (CNNs) [236] and their variants such as dilated causal CNNs [237] also exhibit great success to capture the complex nonlinear relationships among the input sensing data. For supervised learning tasks, the network's parameters will be optimized in an end-to-end manner specifically tailored to the target task (classification, regression, and prediction). For unsupervised learning,

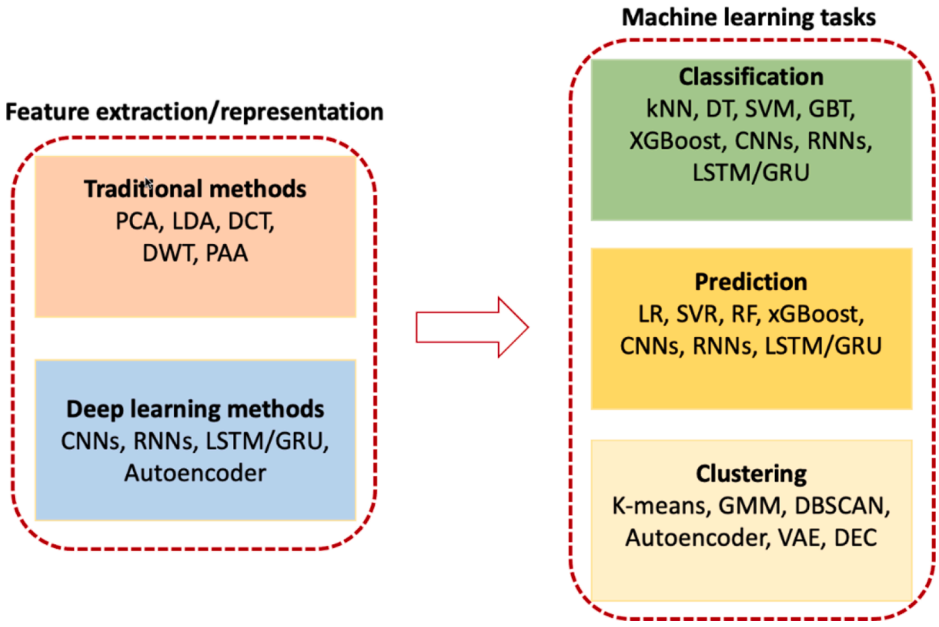

Fig. 13. Representative feature extraction methods and related machine learning tasks for wound healing assessment.

autoencoder (AE) [238] or LSTM based encoder-decoder framework [239] can be employed to obtain a hidden representation of the input sensing data.

5.2. Machine learning tasks

For practical wound healing assessment problems, related machine learning tasks include classification, prediction, and clustering.

5.2.1. Classification

Wound healing classification mainly concerns categorizing the phases or types of wounds. Based on the input raw data or extracted features, many machine learning techniques can be applied to this task. Representative methods include k-nearest neighbor (kNN) [223], decision tree (DT) [223], support vector machine (SVM) [240], Gradient-boosted decision trees (GBDT), and extreme gradient boosting (XGBoost) [241]. For instance, based on dielectric spectroscopy sensors, Rahmani et al. [242] leverage SVM to classify different types of tissue across different samples; In addition, Sattar et al. [224] proposed an IoT based intelligent wound assessment system for the assessment of wound status and use the information gain statistics of decision tree to assess three classes of wound statuses, i.e., good, satisfactory, or alarming. By combining cross-entropy loss with CNNs, wound healing classification can also be conducted in an end-to-end manner [243].

Typical evaluation measures for classification include accuracy, precision, recall, and F1 measure. Specifically, we have

$$Accuracy = \frac{\text{true positive} + \text{false negative}}{\text{true positive} + \text{true negative} + \text{false positive} + \text{false negative}}$$

$$Precison = \frac{\text{true positive}}{\text{true positive} + \text{false positive}}$$

$$Recall = \frac{\text{true positive}}{\text{true positive} + \text{false negative}}$$

$$F1 = \frac{2 \cdot \text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}}$$

5.2.2. Prediction

Wound healing prediction (regression) aims to leverage machine learning algorithms to pursue the relationships between sensing data and the target value [244]. For instance, wound progression researchers have traditionally focused on using piecewise linear regression models for better interpretable results [245]. Traditional regression techniques, e.g., linear regression, logistic regression, support vector regression (SVR) [246], random forest (RF) [223], and XGBoost [241] have been or can potentially be used to estimate wound healing time [247]. In addition, more advanced prediction methods, such as attention-based Long-short Term Memory (LSTM) [248], and dilated casual CNNs [237], and Transformer [249] can also potentially help improve the accuracy of time-to-heal prediction and wound progression trajectory forecasting.

To assess the effectiveness of regression and prediction, mean squared error (MSE), mean absolute error (MAE), and mean absolute percentage error (MAPE) [248], and the coefficient of determination, i.e., R^2 [250] can be used.

5.2.3. Clustering/pattern discovery

When labels are not available for the wound sensing data, it is necessary to explore the underlying patterns and structure of input wound sensing data. In this case, traditional clustering approaches, e.g., k-means [223], Gaussian mixture model (GMM) [223], hierarchical clustering [251], DBSCAN [252], etc., can be applied. For instance, Rahmani et al. [242] leverage GMM to discover 4 categories of wounds based on the electric loss tangent data. Moreover, autoencoder [238], variational autoencoder (VAE) [253], and deep embedding clustering (DEC) [254] are also capable of exploring the more sophisticated non-linear structural relationships among the sensing data.

To measure the effectiveness of clustering, clustering accuracy, purity, mutual information (MI) and normalized mutual information (NMI) could be used [223].

5.3. Close loop control

Based on accurate wound assessment, intelligent wound management and treatment can be conducted to perform close-loop control. For instance, Kiaee et al. [255] showed that the pH value of the local part of wounds can be controlled by a patch via electronic adjustment to release relevant drugs in this part. Zhao et al. [256] designed a wound patch that can precisely control the follow rate in the microfluidic system of

the patch such that the drug release can be adjusted to improve wound healing. Recently, Wang et al. [257] also showed that reinforcement learning can be used to learn a policy to perform patient treatment automatically.

6. Conclusions and outlook

Recent years have seen enormous research effort dedicated to developing sensing and therapeutic systems for wound monitoring and treatment. Various sensing techniques including physical and chemical sensing have revealed the importance of real-time monitoring of various parameters at the wound site for effective treatment of wounds. This review has focused on recent studies dedicated to the monitoring and therapeutic systems for wound healing and wound management. It begins with a review on the physical sensing of temperature, moisture, pressure and strain, and chemical sensing of pH, cytokine, and uric acid. This is followed by a discussion of wound management through on-demand, active drug delivery induced by external stimulations like temperature change, electric field, and light, as well as non-drug stimulations like oxygen therapies and biomechanical cues, to promote wound healing. A data-driven wound healing assessment and management system by leveraging machine-learning and deep-learning frameworks are also detailed. These studies have significantly enhanced next-generation wound healing and management technologies.

Despite significant advances, there is still much to do about effective wound healing and management. In particular, most current wound sensing devices are based on limited types of sensing capabilities. Integrating a wide range of sensors into wound dressings for simultaneous, real-time, high-sensitivity, high-selectivity monitoring of various physical and chemical indicators, including pH, temperature, oxygen level, moisture, mechanical and electrical signals, would provide a wealth of key information for the wound progression. Another important area is incorporating active sensing and precise actuation functions such as drug delivery to enable active responses to variations in the wound environment. To realize effective automated systems, specific markers for regeneration and complications should be identified and targeted. In addition, integrating the active sensing, actuation, with a machine-learning framework to monitor and modulate the healing progression by delivering specific molecules at specific times under the direction of artificial intelligence will accelerate the recovery of the wound. Regarding the machine-learning framework, effectively leveraging and fusing the multimodal sensing data measured with different types of biosensors to make decisions, as well as developing model-agnostic methods to interpret the current black-box models by showing feature importance and accumulated local effect would be very important. Finally, based on accurate wound assessment, how to perform wound management optimally to reduce the healing time and increasing the healing rate is another critical problem to investigate.

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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