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Review

Multimodal bioelectronics: A pathway to digital health management

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https://doi.org/10.1016/j.matt.2025.102048

PROGRESS AND POTENTIAL Multimodal bioelectronics has the potential to revolutionize health management by extending it beyond traditional hospital settings to more flexible and accessible scenarios. Recent innovations in functional materials, advanced manufacturing, and sophisticated sensing technologies have empowered these devices to monitor health conditions seamlessly during daily activities. They facilitate comprehensive disease management through multifactorial analysis, offering a more personalized approach to healthcare. This review delves into the latest advancements in the field, highlighting progress in materials and interface design and exploring energy management strategies and system integration techniques for efficient operation. Furthermore, this review presents case studies of bioelectronics in practical applications for various populations and six major diseases. By continuing to explore these innovations, multimodal bioelectronics paves the way for a digital health management paradigm that is more efficient and accessible to individuals worldwide.

SUMMARY

Recent advancements in multimodal bioelectronics have demonstrated remarkable promise in transforming digital health. In contrast to conventional hospital-based healthcare systems, multimodal bioelectronics facilitates flexible and continuous physiological monitoring, offering the potential for accurate diagnosis and personalized therapeutics. In this review, we summarize and highlight the latest progress in multimodal bioelectronics and their practical applications. We first introduce emerging material selections and interface design strategies for conformal contact with the human body. Then, we discuss the principles of energy management and the workflow of integrated platforms, especially introducing algorithm utilization for real-time data acquisition, processing, and transmission. Additionally, we focus on the categorized practical applications of multimodal bioelectronics in digital health by emphasizing their role in the healthcare of specific populations, as well as in the diagnosis and monitoring of common diseases. Finally, we provide an outlook to address the challenges and the trends of multimodal bioelectronics toward digital health management.

INTRODUCTION

The human body functions as a sophisticated multimodal information platform, with the operations of its eight systems clearly reflected through body fluids, heat conduction, and electrical signals. Traditional healthcare methods involve in-person doctor consultations, medication, blood tests, and imaging diagnostics, while these approaches normally rely on large equipment and skilled operators, with specific environments and potential risks. Personalized healthcare is largely limited by the current hospital-centric medical paradigm, primarily due to its time-consuming and high cost issues. The emerging concept of digital health has been introduced to emphasize data-driven medical decisions,[1] by leveraging bioelectronics, telemedicine, and mobile applications to make healthcare more accessible and efficient for a broader population. With the real-time collection and analysis of physiological signals, digital health technologies can deliver personalized health management solutions.[2,3] The cooperation with big data and artificial intelligence further allows early detection of potential health issues with preventative care.[4–6]

Multimodal bioelectronics is an advanced electronic platform that contains two or more functionalities to interact with biological systems.[7,8] It encompasses the use of multiple sensing modalities for acquisition of acquire biological information, electronic devices for signal transmission, and computational tools for data processing, ultimately advancing digital health management. Therefore, multimodal bioelectronics has attracted huge

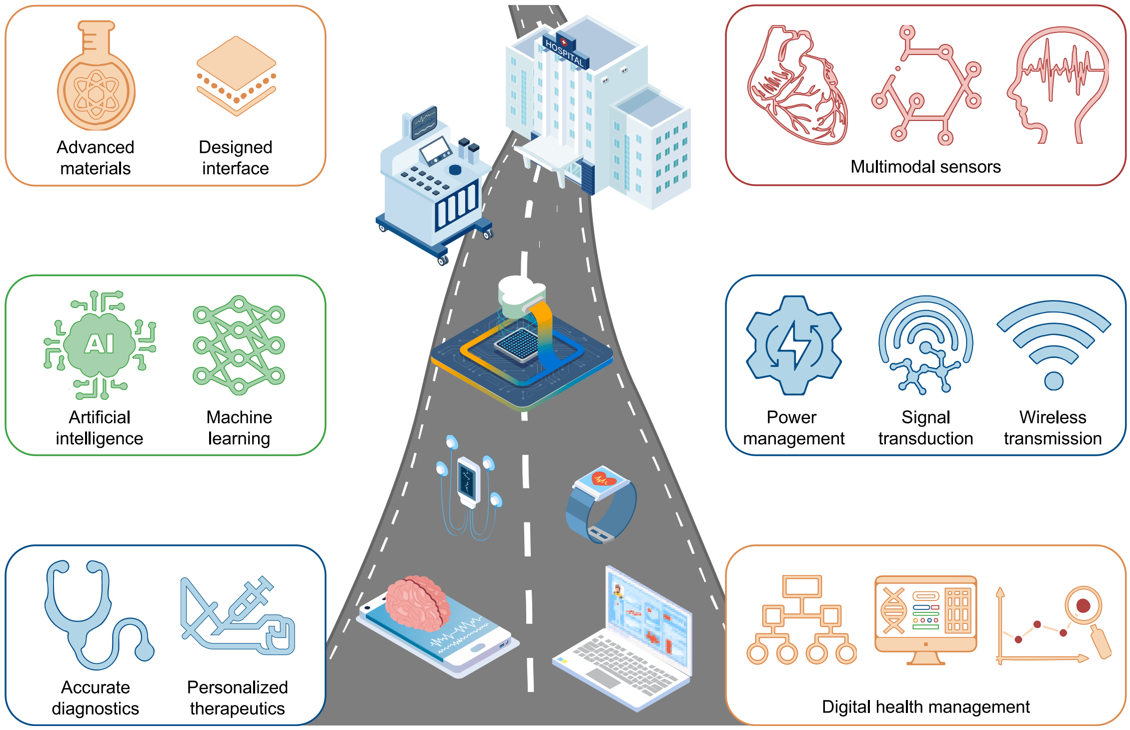

Figure 1. Multimodal bioelectronics paving the way for digital health management

attention as a powerful medium to meet the growing demands of digital health solutions for human well-being.[9] First, unlike traditional hospital-based healthcare, wearable or implantable bioelectronics enable convenient detection across daily activities in multiple scenarios like home, workplace, and outdoors. Second, multimodal bioelectronics can simultaneously monitor biophysical,[10] biochemical,[11] and electrophysiological signals,[12,13] providing a comprehensive perspective on complicated medical conditions. Third, bioelectronics has innovated the traditional concept of single-function devices into integrated platforms, combining sensing components, signal processing units, and energy management modules, without further connected equipment.[14,15] Finally, bioelectronics could incorporate with treatment methods, such as electrical stimulation, phototherapy, thermotherapy, and microbial modulation,[16] paving the way for personalized closed-loop health management and practical applications in population-level digital health.[17]

With rapid advancements in fundamental chemistry, materials science, and biomedical engineering, multimodal bioelectronics has achieved remarkable progress over the past decade. This review highlights the latest evolutions in wearable and implantable multimodal bioelectronics with practical applications in digital health (Figure 1). We begin by summarizing advanced materials and interface design strategies to develop biocompatible devices with high sensitivity and long-term stability; then discuss the working principles of energy harvesting, energy storage, signal sensing and transmission, and the critical role of data processing with advanced algorithms from a system-level perspective. To explore systematic design approaches for multimodal bioelectronics, we analyze recent representative applications regarding health characteristics of three specific populations to illustrate the adaptive capabilities of bioelectronics. In the context of patient-centric health management, we focus on six categories of common diseases, such as cardiovascular diseases and mental disorders, discussing their physiological and psychological information in detail. Finally, we present insights into the challenges and future directions of multimodal bioelectronics in digital health, paving the way for its continued evolution.

ADVANCES IN MATERIALS FOR BIOELECTRONICS

The advancement of wearable or implantable bioelectronics has been profoundly impacted by the rapid development of materials science. In terms of practical applications, the properties of materials in close contact with skin or living organisms are receiving increasing attention to enhance the functionality, including stretchability, flexibility, conformability, mechanical durability, biocompatibility, and breathability. Different from traditional rigid electronics, flexible bioelectronics leverage innovative materials such as metals, inorganic materials, organic materials, polymers, and composites, as summarized in Table 1.[18–57]

Inorganic materials

Inorganic materials, such as metals, metal oxides, and semiconductors, have been at the forefront of bioelectronics because of the high conductivity, stability, and mechanical strength. Some novel inorganic materials are emerging in flexible bioelectronics, such as MXene, families of transition metal carbides or nitrides in two-dimensional (2D) nanomaterials, which possess a 2D

Table 1. Summary of materials in multimodal bioelectronics

Types	Representative materials	Advantages	Limitations	Reference
Transition metal carbides/nitrides	MXene	excellent electrochemical properties, tunable chemical characteristics, scalability	prone to oxidation, poor dispersion, low mechanical strength	Wu et al.,[18] Huang et al.,[19] Cao et al.,[20] Karbalaei Akbari et al.,[21] and Bi et al.[22]
Carbon-based materials	CNT, graphene, graphene oxide	electrical and thermal conductivity, mechanical stability	poor dispersion	Darshna et al.,[23] Li et al.,[24] Lu et al.,[25] Liu et al.,[26] and Wang et al.[27]
Liquid metal	Ga–In, Ga-Cu	conductivity, scalability	prone to oxidation, high cost, complex processing	Xu et al.,[28] Cao et al.,[29] Chung et al.,[30] Kwon et al.,[31] Li et al.,[32] and Yu et al.[33]
Metal nanomaterials	Au nanoparticles, Ag nanowires	electrical and thermal conductivity, mechanical flexibility, optimization through morphology control	high cost, complex processing, poor long-term biocompatibility	Ha et al.,[34] Kang et al.,[35] Xu et al.,[36] Choi et al.,[37] and Jiang et al.[38]
Conductive elastomers	silicone rubber-based conductive composites, polyurethane-based conductive composites, Ag-Au/SBS	flexibility, stretchability, performance tunable by adjusting filler content	inconsistent conductivity, poor fatigue resistance	Cuttaz et al.,[39] Zhao et al.,[40] Xu et al.,[41] and Gu et al.[42]
Conductive polymers	PEDOT:PSS, PPy, PANI	adjustable electrical properties	poor processibility, processing complexity	Tseng et al.,[43] Nasser et al.,[44] Heck et al.,[45] Taussig et al.,[46] and Gao et al.[47]
Hydrogel	PAAm, PEG, PEDOT:PSS/PVA	flexibility, stretchability, biocompatibility, ease of chemical modification, degradability	low mechanical strength, prone to dehydration, poor long-term stability	Yao et al.,[48] Han et al.,[49] Dai et al.,[50] Li et al.,[51] and Li et al.[52]
Ionogel	ureido-pyrimidinone-grafted imidazolium, acrylonitrile/ethyl acrylate/1-ethyl-3-methylimidazolium bis (trifluoromethylsulfonyl)imide	high ionic conductivity, flexibility, transparency, chemical stability	low mechanical strength, poor long-term stability	Luo et al.,[53] Zhao et al.,[54] Li et al.,[55] He et al.,[56] and Shi et al.[57]

"honey-comb-like" lattice structure.[58] Monolayer MXene exhibits strong mechanical properties, while multilayer MXene allows for easy design and customization with diverse composition and structure. Introducing metal ions in MXene nanolayers can eliminate electrostatic repulsion, further enhancing interlayer interactions and the arrangement of the nanosheets. Recent study of MXene fibers has achieved impressive performance in mechanical strength and electrical conductivity.[20] With the wet spinning process, the assembled Zn^{2+}-crosslinked MXene fibers are suitable for flexible textile devices. As shown in Figure 2A, the oriented sheet-like structure of MXene fibers allows achievement of bipolar amplification for sound pressure sensing. The fabrication of microfiber electrodes faces challenges in terms of large-scale deployment. However, by leveraging the ease of processing MXene coatings, nylon filaments offer both handling and consistent results, especially when cut at the tip. This approach facilitates the production of electrodes in various lengths, demonstrating exceptional scalability at both cellular and tissue levels.[22]

Carbon-based materials, such as graphene and carbon nanotubes (CNTs), have attracted extensive interest due to their excellent properties including lightweight, thermal stability and mechanical strength. The superior electrical conductivity makes them ideal candidates as electrodes.[59] CNTs, with great electrochemical performance, are competent in electrical stimulation and recording with low tissue contact impedance, performing long-term monitoring of neural activity up to several weeks.[60] Moreover, the high thermal conductivity allows CNTs embedded in insulating substrates to create stretchable heating films or textiles (Figure 2B).[26]

As another promising candidate, liquid metal is also suitable for soft and stretchable bioelectronics. It can withstand large strains without losing conductivity due to solid-liquid phase transitions and plastic deformation. By cooling a gallium-indium alloy and encapsulating it in an elastomer, the resulting strain sensor is capable of monitoring finger movements (Figure 2C).[32] Metallic nanowires with intrinsic stretchability and conductivity are commonly used to form conductive percolation networks. Recent studies proposed that *in situ* phase separation can assemble silver nanowires (AgNWs) on porous polymer surfaces, achieving ultra-low percolation thresholds and significant conductivity.[36] Figure 2D shows a high-resolution (~50 μm) patterned AgNW electrode, allowing strain-insensitive stretchable circuits in health-related electronic applications like electromyography (EMG) recording.[61] Furthermore, inorganic materials with unique properties have been extensively studied. For instance, optoelectronic materials such as perovskite scintillators were explored for fast-response radiography, realizing portable X-ray imaging under sunlight.[62,63] Magnetic materials like NdFeB microparticles contribute to the development of non-contact magnetic skins,[64] achieving super-resolution perception and promising potentials in intelligent control.

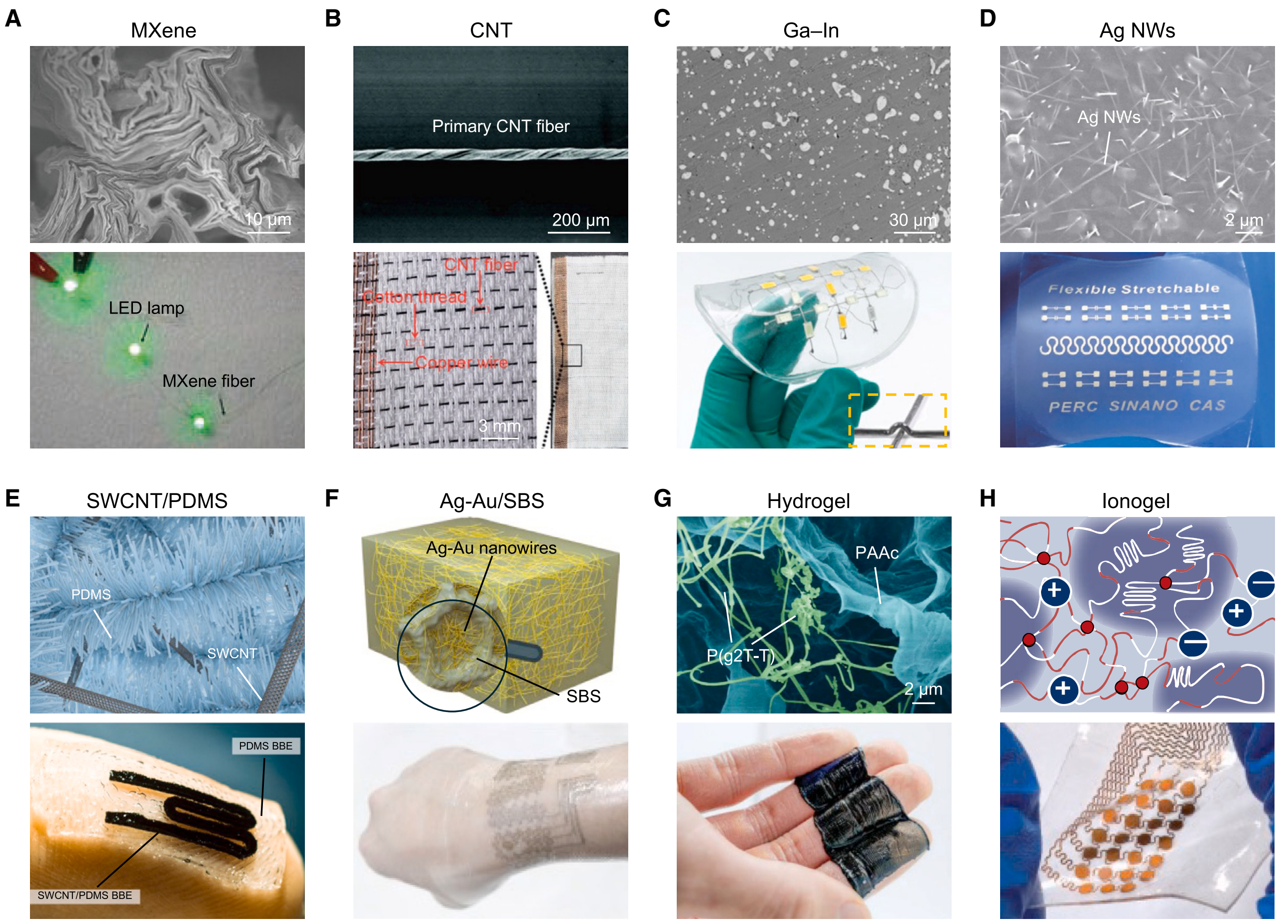

Figure 2. Advanced materials for bioelectronics

(A) Zn-MXene fibers with ideal mechanical strength and flexibility while preserving high conductivity.
(B) The primary CNT fiber and the heating textiles with excellent mechanical and heating properties.
(C) 3D structured Ga–In solid wire for flexible bioelectronics.
(D) AgNWs patterned stretchable electrodes.
(E) Ultrasoft and conductive PDMS bottlebrush elastomer composite with single-wall carbon nanotubes as conductive fillers.
(F) Microstructured Ag–Au nanowire nanocomposites dispersed in poly(styrene-butadiene-styrene) elastomer.
(G) Hydrogel semiconductors prepared by p(g2T-T) and acrylic acid.
(H) Humidity-insensitive flexible iontronic pressure sensor array based on a tough ionogel with two hydrophobic phases.

Composite materials

To overcome the limitation of individual materials, composite materials, which combine the synergistic effects of different components, have gained significant attention in recent years. As shown in Figure 2E, a bottlebrush-like elastomer (BBEs) filled with single-wall carbon nanotubes (SWCNTs) revealed mechanical flexibility of polymers with the conductivity and stability of inorganic fillers. The tissue-matched low Young's modulus of BBEs comes from highly branched architecture, ensuring good pressure sensitivity for wearable sensing.[41] Another representative example to trade off between conductivity and stretchability is metallic nanostructured materials in polymer matrix. Figure 2F shows Au-coated AgNWs dispersed in poly(styrene-butadiene-styrene) (SBS) elastomer, the resulting soft bioelectronics can be conformally integrated with both skin and heart for continuous electrophysiological recording, and electrical and thermal stimulation.[37]

Hydrogels, consisting of water-saturated crosslinked polymer networks, have been widely studied in the fields of bioelectronics.[65] High water content imparts remarkable properties, enabling seamless interface between biological tissues and bioelectronics. Primarily, the tissue-like mechanical strength ensures adhesiveness and biocompatibility, which is paramount in both wearable and implantable applications.[66,67] Second, the notable flexibility mitigates mechanical mismatch and enhances stability in electrical and biological performance. Furthermore, the wet and ion-rich environments allow for multifunctional design through chemical modifications. For bioelectronics, enhancing the conductivity remains a significant challenge for hydrogels. Highly conductive hydrogels, such as pure PEDOT:PSS, offer struggle with poor stretchability and stability. A promising solution to address these limitations is the development of a double-network conducting polymer hydrogel, combining PEDOT:PSS with polyvinyl alcohol. Through an *in situ* aggregation and densification method, this hydrogel achieves impressive stretchability of up to 150%, while maintaining long-term stability for EMG signal recording *in vivo*.[51] Traditional hydrogels have typically served as insulators or conductors, while by combining N-type semiconductors with polymers, a semiconducting hydrogel was constructed (Figure 2G). This hydrogel exhibits good electron mobility and high on-off ratios, allowing to amplify electrophysiological signals in bioelectronic applications.[52]

Ionogels are an intermediate type of gel situated between hydrogel and organogel, with ionic liquids as their primary component.[56,68] Considering that ion-electronics-based sensing array devices offer superior sensing performance, humidity-insensitive ionogels are suitable for implantable medical applications to address the issue of performance degradation in ionogels caused by moisture absorption.[57] In addition to overcoming the limited functionality of single materials, composite materials can enhance interactions between different materials, achieving seamless integration between soft and rigid components.[38]

SOFT-HARD INTERFACE DESIGN

To integrate bioelectronics into daily or medical health management, it is essential to create a seamless and imperceptible human-machine interface. First, electronic interfaces that contact the human epidermis or internal tissues should be non-toxic, non-irritating, and non-allergenic, which necessitates the selection of highly biocompatible materials. Second, to enhance wearing comfort and detection efficiency, conformability to irregular or wrinkled surfaces is fundamental for flexible bioelectronics. Last, adhesion at soft-hard interfaces is crucial, with the challenge of balancing the adhesive strength during device removal to prevent excessive adhesion to cause harm on the body.

Skin-interfaced bioelectronics

Wearable bioelectronics have been used to monitor epidermal pressure, cardiac activity (i.e., electrocardiograms [ECGs]), brain activity (i.e., electroencephalograms [EEGs]) and muscle activity (i.e., electromyogram [EMGs]).[69] On the head, due to the presence of hair and the delicate nature of the scalp, wet interfaces are considered reliable for EEG detection. A representative example is the use of biogels as electronic interfaces to establish conformal contact between the electrodes and the hair-covered scalp. Figure 3A shows the signals acquired by the biogel along with a comparison of signals detected by a commercial device, demonstrating effectiveness and reliability.[70] On the skin interface, it is required to balance conformal adhesion and easy peel-ability. Skin temperature-triggered adhesive polymers are considered an ideal material, which is rigid and non-adhesive at room temperature but becoming soft and adhesive at epidermal temperatures with two distinct stages (Figure 3B).[71] Another ingenious interface construction approach is about iontronic devices, where the synthesis and packaging of the device are simplified by incorporating ionic transport within the human body as part of the mechanism. In this context, a skin-electrode mechanosensing structure is constructed, consisting of a sensing electrode, a conformable counter electrode, and skin as an ionic material (Figure 3C). The microstructured electrodes are laminated on the skin using a piece of transparent and breathable healthcare film for long-term monitoring of patient vital signs.[72]

Tissue-interfaced bioelectronics

Implantable bioelectronics have higher demands for interfaces, as the absence of epidermal protection makes human organs and tissues softer and more fragile, with immune rejection and device transmission efficiency even more critical. In the brain, intracortical probes have become essential tools in neuroscience research, but traditional high-modulus metal materials can lead to chronic inflammatory responses. Temperature-responsive shape-memory polymers could create expandable cortical probes, which establish a more stable neural interface. These probes feature a foldable, fishbone-like structure, with each branch element containing a sensing electrode. When inserted into the cortical tissue, the branches deflect toward the main shaft and lock in place, minimizing tissue trauma. After implantation, the folded probe branches autonomously transform into a tissue-like conformability, providing long-term stable neural signal monitoring (Figure 3D).[73] In addition, cardiac monitoring is one of the most important metrics for health conditions. Bio-adhesive devices for the heart need to provide rapid, non-irritating tissue adhesion while preventing performance degradation of the sensing elements due to repeated strain. One example is the bioelectronic patch that achieves quick adhesion and small resistance change after long-term strain. As shown in Figure 3E, this patch successfully measured long-term ECG signal in awake rats.[74] Furthermore, vascular implants for the treatment of ischemic cardiovascular diseases are also impressive. In blood vessels, a 3D-printed fibrin patch with endothelial cell patterns can promote the infiltration and integration of small collateral vessels, thereby generating functional blood vessels. In Figure 3F, this patch was implanted in an ischemic model of resected femoral artery, demonstrating a significant increase in blood perfusion levels in the ischemic limb after 5 days.[75]

Soft-hard interface design is fundamental to the usability of bioelectronics, ensuring effective sensor operation and accurate signal acquisition. The development of conformal and functional interfaces, utilizing advanced materials and fundamental physical and chemical principles, has become the central focus in bioelectronics. Wearable and implantable bioelectronics gain significant advantages from innovative interface design. For wearable bioelectronics, the interface provides comfort and flexibility with continuous monitoring of physiological information, and for *in vivo* scenarios, the stability of interface between bioelectronics and tissues or organs allows for dynamic tracking.[76,77] However, challenges such as signal noise, durability, and long-term stability should be addressed to prevent secondary injuries and minimize the rise of immune rejection and toxicity.[78]

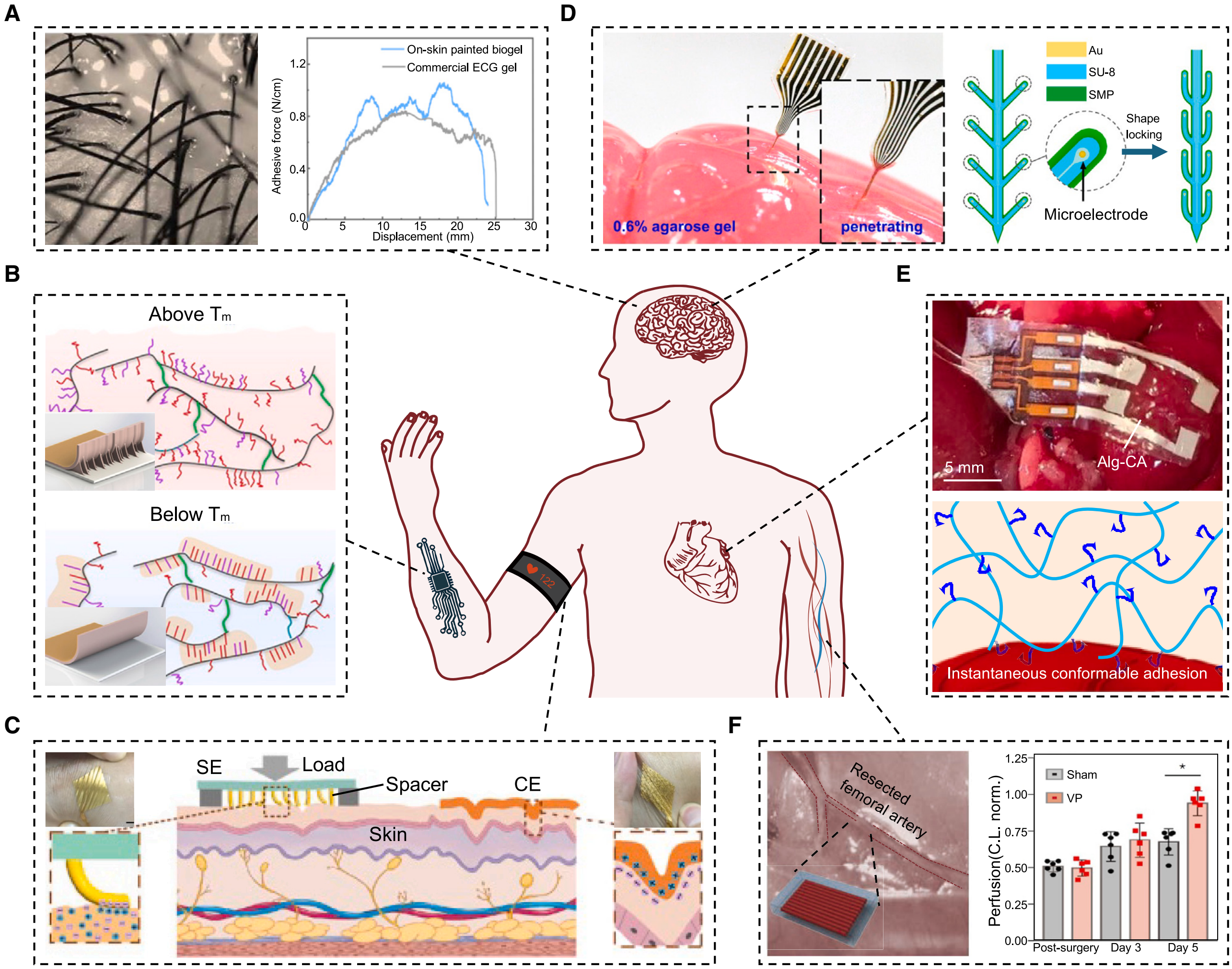

Figure 3. Soft-hard interface design for bioelectronics

(A) On-skin paintable biogel interface for EEG recording.

(B) The mechanism of bistable adhesive polymer with skin temperature-triggered conformal adhesion.

(C) The illustration of skin-electrode with mechanosensing structure.

(D) A mechanically adaptive and deployable intracortical probe with branching electrodes on a temperature-responsive shape memory polymer substrate.

(E) A bioelectronic patch with instantaneous and conformable tissue adhesion on a heart for precise cardiac monitoring.

(F) A fibrin patch with patterned endothelial cells promotes perfusion and rescue function of ischemic tissues.

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SYSTEM INTEGRATION OF BIOELECTRONICS

Compared to bulky and stationary hospital devices, the portability of multimodal bioelectronics offers a key advantage primarily due to its small size, light weight, and compact system integration. It enables continuous monitoring and precision treatment without the limitation of time, location, or the need for constant supervision by medical professionals. Besides multimodal biosensing, system integration includes power management and backend data processing to provide real-time information regarding health management. This section summarizes principles and commonly used strategies for energy harvesting and energy storage, as well as the methods and tools for data processing and analysis.

POWER MANAGEMENT FOR BIOELECTRONICS

To maintain the continuous operation of bioelectronics with stable power supply, the power management module relies on efficient energy harvesting and reliable energy storage. Energy harvesters convert biochemical energy, mechanical energy, light, and thermal energy from the accessible power sources into electricity, which is subsequently stored in energy storage devices such as batteries and supercapacitors (Table 2).[79–109]

Table 2. Summary of energy devices in multimodal bioelectronics

Energy devices		Advantages	Limitations	Outputs	Reference
Energy harvesters	BFCs	high biocompatibility, on-body available	limited lifespan, sensitivity to environmental conditions	a few mW cm^{-2}	ul Haque et al.,[79] Wu et al.,[80] Katz et al.,[81] Huang et al.,[82] and Maity et al.[83]
	TENG	flexibility and lightweight, broad material choices	low energy, sensitivity to humidity	μW to mW cm^{-2} μW to mW g^{-1}	Cheng et al.,[84] Niu et al.,[85] Wu et al.,[86] Huang et al.,[87] and Wang et al.[88]
	solar cell	high energy density, renewable energy source, long operational life, scalability	dependent on light availability	a few tens of mW cm^{-2}/W g^{-1}	Liu et al.,[89] Jinno et al.,[90] Hu et al.,[91] Cheng et al.,[92] and Kaltenbrunner et al.[93]
	TEG	long lifespan	low efficiency, limited power output	~μW cm^{-2}/W g^{-1}	Yang et al.,[94] Sattar et al.,[95] Hinterleitner et al.,[96] Li et al.,[97] and Zhang et al.[98]
Energy storage devices	supercapacitor	rapid charging/discharging, long cycle life	low energy density	up to 10,000 mW g^{-1}	Li et al.,[99] Wang et al.,[100] Jiang et al.,[101] and Ling et al.[102]
	rechargeable battery	stable voltage output	low energy density	hundreds of mW g^{-1}	Zhu et al.,[103] Mackanic et al.,[104] Yue et al.,[105] Yoo et al.,[106] Ma et al.,[107] Zhong et al.,[108] and Lu et al.[109]

Energy harvesting strategies

Biofuel cells (BFCs) convert chemical energy from fuels (such as glucose, fructose, lactate, etc.) into electrical energy through biochemical reactions. As shown in Figure 4A, BFCs consist of a bioanode, biocathode, and electrolyte. In redox reactions, electrons are transferred to the external circuit, generating current and power.[82] The transient response capability, open circuit potential, and energy density of BFCs are critical indicators. High-efficient BFCs have been proven to power the whole biosensing system and human-machine interaction.[110] Besides biochemical energy harvesting, triboelectric nanogenerators (TENGs) operate based on electrostatic induction principles and the triboelectric effect. During the contact-separation process, triboelectric charges with opposite polarities accumulate on their surfaces (Figure 4B), thus converting minute mechanical energy into electricity.[111] Subtle pressure variations caused by body movements such as muscle activity,[88] breathing,[112] heartbeat,[113] and blood flow[114] can effectively drive TENGs, making them highly suitable as power sources for portable bioelectronics.

For an ambient environment, solar cells convert light into electricity through photovoltaic effect. Composed of electrodes, active layers, and carrier-selective layers, they generate electron-hole pairs under light irradiation, which are separated and collected to produce electricity (Figure 4C).[92] Ultra-thin, highly flexible perovskite solar cells have demonstrated a power density of 23 W g^{-1}, showcasing their potential for lightweight and portable applications.[93] According to the Seebeck effect, thermoelectric generators (TEGs) can convert heat into electricity. A temperature difference between two nodes in a conductor or semiconductor causes charge carriers to flow, generating thermoelectric voltage and direct current (Figure 4D). The conversion efficiency of thermoelectric materials depends on the Seebeck coefficient, electrical conductivity, and thermal conductivity.[96,97] Within small temperature differences, TEGs produce considerable power output to operate sensors and wireless transmission modules required in wearable scenarios, which generate a voltage of 10 mV under a 10 K temperature gradient to improve the viability of fibroblast cell and drive the expression of growth factor, accelerating wound healing rate.[98] These strategies, along with piezoelectric generators,[87,115–117] magnetoelectric generators,[118] and microbial fuel cells,[119] enable sustainable energy collection, enhancing the functionality and autonomy of bioelectronics for sensing process and practical applications.

Energy storage techniques

When the energy source is intermittent or fluctuating, energy storage systems are crucial for ensuring a persistent and stable power supply. Supercapacitors store energy electrostatically using current collectors, electrodes, a separator, and an electrolyte. During the charging process, electrostatic forces attract negative ions to the positive electrode, forming a double layer of charge to store energy (Figure 4E). To overcome mechanical mismatches caused by stretching and twisting in flexible devices, the integration of electrodes, gel electrolytes, and separators into flexible substrates provides an effective solution for supercapacitors.[102] Rechargeable batteries store energy through reversible electrochemical redox reactions (Figure 4F), where electricity is stored through quantities of materials within the electrodes, endowing large charge storage capacity. Flexible Zn–air batteries based on hygroscopic conductive hydrogels achieve energy density of up to 246 Wh kg^{-1}, and wearable batteries formed with polymer gel electrolytes demonstrate energy densities of 128 Wh kg^{-1}.[108,109] Supercapacitors and rechargeable batteries are the most

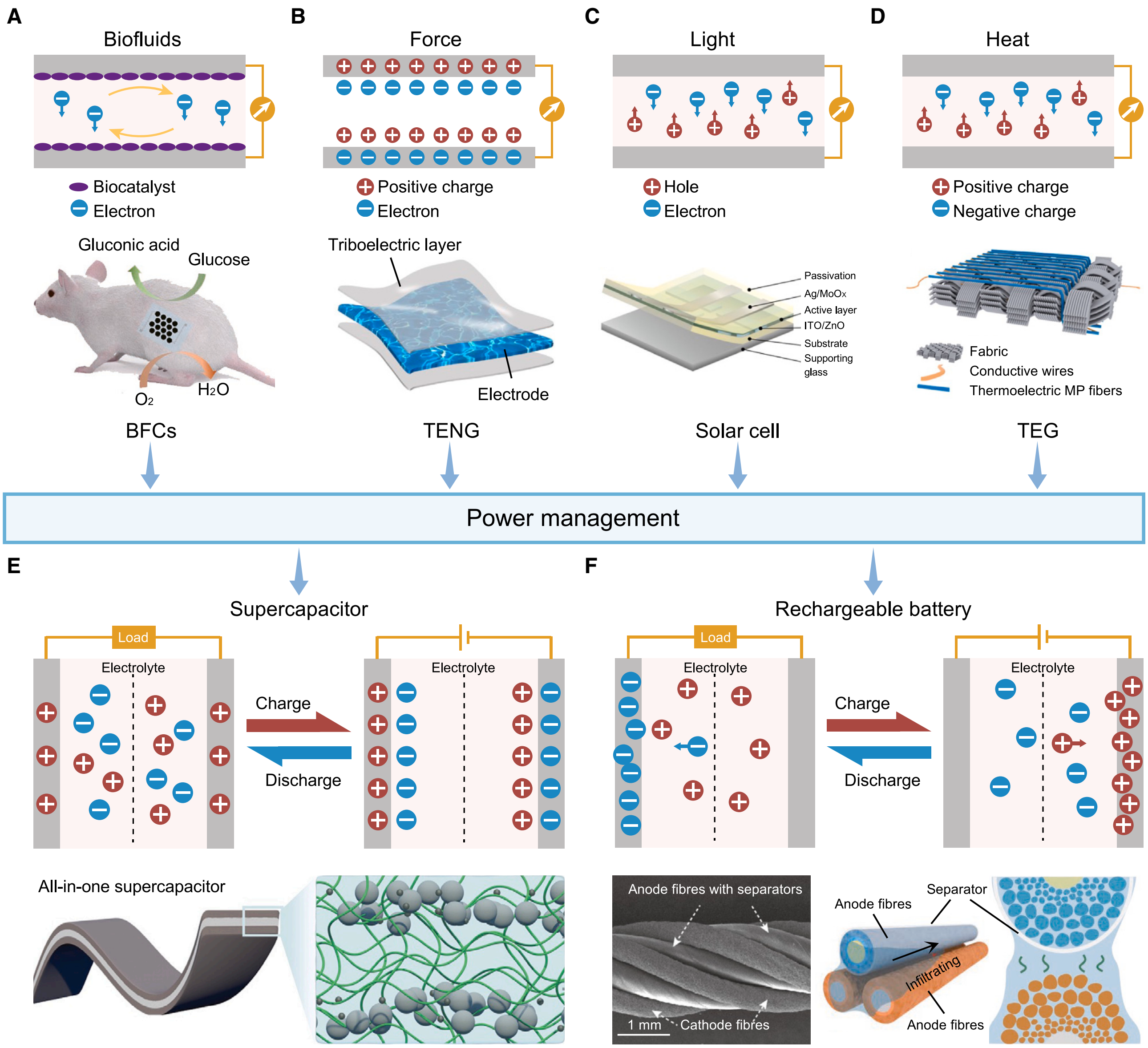

Figure 4. Working principles of energy harvesters and energy storage devices for power management

(A) In biofuel cells (BFCs), the fuel is oxidized and reduced by biocatalyst in the electrolyte to generate power output.

(B) In triboelectric nanogenerators (TENGs), triboelectric charges with opposite polarities accumulate on surfaces during the repeatable contact-separation process.

(C) In solar cells, light irradiates the active layer, generating electron-hole pairs that are separated by the electric field and collected by carrier-selective layers and electrodes.

(D) In thermoelectric generators (TEGs), charge carriers flow because of temperature difference to generate thermoelectric voltage.

(E) In supercapacitors, negative ions move to the positive electrode and positive ions move to the negative electrode during charging process.

(F) In rechargeable batteries, reversible electrochemical oxidation-reduction reactions happen to store and release electricity.

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common storage strategies for long-lasting self-powered devices. The construction of flexible electrodes, stability of electrochemical performance during bending and folding, along with high energy density are key challenges for energy storage devices in bioelectronics.

DATA PROCESSING AND BACKEND ANALYTICS

High-quality physiological signals related to health conditions are critical for successful implementation of multimodal bioelectronics, where they can be classified into biophysical,

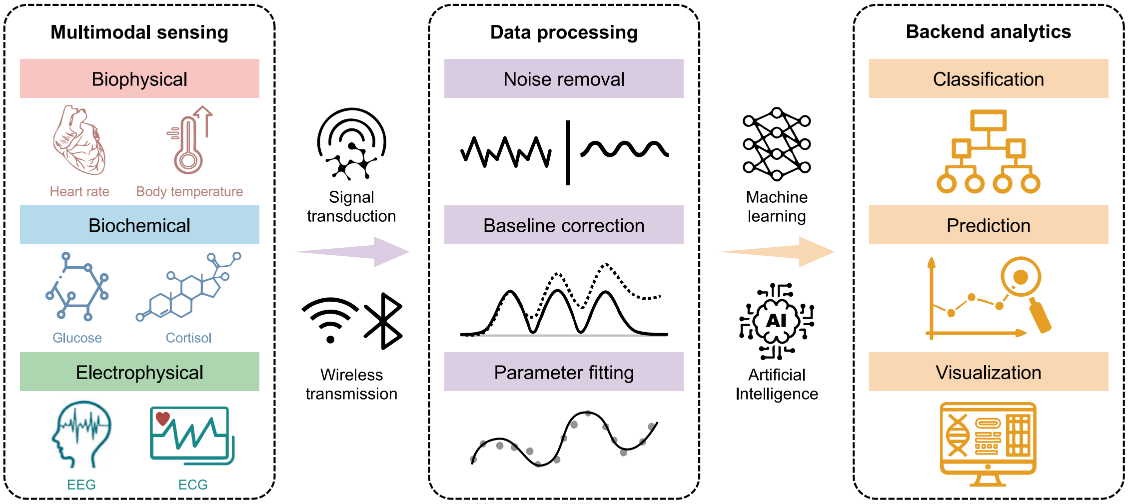

Figure 5. Workflow diagram of bioelectronics with multimodal sensing, data processing, and backend analytics

biochemical, and electrophysiological signals. As shown in the system flowchart (Figure 5), multimodal biosensors can acquire raw data from the human body, which can be converted into electrical signals and transmitted wirelessly to user interfaces such as smartphones or computers. Physiological activities and body movements can introduce motion artifacts, which may compromise the accuracy and stability of sensing signals.[120] In terms of material design, it is essential to consider the compatibility of multilayer materials to avoid obstacles for electron and ion transport. For interface design, stable adhesion can mitigate interference from biomechanical activities, reducing mechanical motion artifacts. A seamless interface minimizes the risk of detachment or displacement, preventing changes in electrode contact. To enhance anti-interference capabilities during signal acquisition, reducing the number of connecting wires in bioelectronics is a potential solution as well. In addition, biopotential motion artifacts, generated by stimulated nerves or muscles through cellular electrochemical activity, may interfere with target signal acquisition. Therefore, it is critical to design independent monitoring principles for target signals. And in post-processing, techniques such as noise removal and baseline correction are essential to address inevitable motion artifacts and electromagnetic signal interference. Parameter fitting, short-time Fourier transform, signal smoothing, and feature extraction are common techniques to normalize the intensity, determine the peak amplitude, and specify the sensitivity accordingly. Coming to backend analytics, artificial intelligence-assisted machine learning (ML) algorithms have rapidly emerged as powerful tools.[121,122] ML can be applied to fields such as bioinformatics, pattern recognition, data analysis, and mining.[123] For high-throughput samples, AI-based ML can adjust the dynamic range of each channel to match the characteristics of specific biomarkers, thus enhancing detection accuracy and providing specific diagnostics.[124] One example is that ML can be used to extract features from routine blood tests and biochemical data, enabling the predictive model construction for cardiovascular diseases.[125] In the typical field of multimodal sensing-stress response monitoring, information such as vital signs and sweat molecular biomarkers could be classified and quantified through an ML pipeline, which has proven to outperform traditional subjective assessments and questionnaires.[11] For users, advanced ML could analyze data through adaptive feedback loops with behavior analysis, predictive indicator modeling, report visualization, and personalized medical recommendations, thus proposing a complete closed-loop healthcare solution.[126] The collection of large amount high-quality physiological signals can significantly enhance the scale and quality of signal databases, thereby improving the performance of ML to associate the connections between physiological information and health conditions. The density of computing devices in bioelectronic systems should be increased to enable larger-scale algorithms and more advanced neural networks.

CASE STUDIES OF DIGITAL HEALTH MANAGEMENT

Modern healthcare concepts are no longer limited to in-hospital treatments, while increasingly focusing on daily monitoring and post-treatment healthcare. Recording and analyzing routine physiological data can enhance clinical diagnosis and shorten treatment durations. Portable, unobtrusive multimodal bioelectronics are set to become the "family doctor," especially for at-home settings and real-time communications. By population feature extraction, special groups require specific management or long-term medical care with accurate and instant feedback, including vulnerable individuals like neonates, high-risk occupational groups like athletes, and astronauts. Meanwhile, for the health management of common diseases, including skin diseases, respiratory diseases, digestive disorders, cardiovascular diseases, neurological disorders, and mental disorders, multimodal bioelectronics has brought alternative approaches covering from continuous monitoring to precision treatment (Table 3).[3,11,15–17,127–161]

Table 3. Summary of multimodal bioelectronics in digital disease management

Types	Representative diseases	Representative physiological information	Advantages	Limitations	Reference
Skin diseases	psoriasis, atopic dermatitis, eczema	skin temperature; pH, inflammatory markers (e.g., cytokines); EDA	continuous monitoring, personalized treatment	limited penetration depth for deep tissue treatment	Shi et al.,[16] Chun et al.,[127] Baik et al.,[128] Long et al.,[129] Li et al.,[130] and Qian et al.[131]
Respiratory diseases	COPD, asthma, pulmonary fibrosis	respiratory rate; VOCs in breath; diaphragm EMG	real-time monitoring, early disease detection	accuracy challenges, discomfort with prolonged use	Liu et al.,[132] Kwiatkowski et al.,[133] Wang et al.,[134] Lee et al.,[135] Heng et al.,[136] Wang et al.,[137] Li et al.,[138] and Suo et al.[139]
Digestive system diseases	anastomotic leaks, inappetence, irritable bowel syndrome	gastrointestinal muscle activity; trimethylamine N-oxide (TMAO), trimethylamine (TMA); gastric electrical activity	targeted diagnostics, personalized treatment	limited battery life for ingestible devices, biosafety	Sánchez-Tirado et al.,[140] Sánchez-Tirado et al.,[141] Zhang et al.,[142] Liu et al.,[143] Nan et al.,[144] and You et al.[145]
Cardiovascular diseases	high blood pressure, reentrant arrhythmias, atherosclerosis	heart rate, blood pressure; blood glucose; ECG	continuous real-time data, emergency alerts	risk of infection for implants, potential for false alarms	Li et al.,[3] Wang et al.,[146] Park et al.,[147] Han et al.,[148] Sunwoo et al.,[149] Zhou et al.,[150] and Fullenkamp et al.[151]
Neurological disorders	stroke, epilepsy, Alzheimer's disease, Parkinson's disease	brain oxygenation, intracranial pressure; Neurotransmitters; EEG	precise brain signal monitoring	ethical concerns about neural data privacy	Li et al.,[152] Liu et al.,[153] Minev et al.,[154] Matrone et al.,[155] Tang et al.,[156] and Hu et al.[157]
Mental disorders	anxiety disorder, post-traumatic stress disorder, schizophrenia	heart rate variability; sleep patterns; cortisol; vagal nerve activity	avoid subjectivity	regulatory challenges	Xu et al.,[11] Torrente-Rodríguez et al.,[15] Oh et al.,[17] Tang et al.,[158] Yang et al.,[159] Pei et al.,[160] and Ok et al.[161]

DIGITAL HEALTHCARE FOR SPECIAL POPULATIONS

Even in the absence of illness, individuals with specific occupational risks or those unable to care for themselves require continuous monitoring and personalized healthcare. In comparison with traditional methods, multimodal bioelectronics provides an optimal solution, offering comprehensive, real-time monitoring and support tailored to their unique needs.

Neonates

Neonates, as a highly vulnerable population, are particularly sensitive to rigid interfaces of medical devices. A "skin-like" vital sign monitoring system has been established to minimize the potential damage caused by bioelectronics. As illustrated in Figure 6A, an ECG epidermal electronic system (EES) is deployed on the chest of a neonatal doll, while a photoplethysmogram epidermal electronic system (PPG EES) is positioned on the foot. Through multimodal sensing, this dual-node measurement setup can extract several vital indicators,[162] realizing comparable recording performance with gold standard. However, there remains a gap in the evolution of intelligent monitoring for common neonatal diseases. For example, a fluorescent dermal nano-tattoo enables minimally invasive and continuous monitoring of bilirubin related to jaundice in interstitial fluid.[163] The assessment of infant brain development can be achieved through general movements analysis. A sparse sensor network, combined with an AI-based algorithm, enables reliable early diagnosis of developmental disorders.[164] In addition to avoiding iatrogenic injuries and continuous monitoring, the medical care of neonates focuses on eliminating barriers to parent-child contact, bringing it from the hospital to the bedside. Through the Internet of Things and digital interaction, it is possible to analyze and master every movement of newborns non-invasively and remotely.[165]

Athletes

For athletes with vigorous movements and excessive sweat, the biggest challenge of bioelectronics is the weakness in adhesion. To eliminate the interference of motion artifacts, the device should consistently exhibit strong conformality with the natural skin. Hydrogels or ionogels are currently the most compatible materials for soft compliance with biological tissues. An *in situ* generated hydrogel interface can establish a highly conformal interface on curved biological surfaces without auxiliary adhesives and maintain synchronized motion with the deforming skin. This approach not only enables detection of both significant and subtle body movements within a short response time but also ensures the capture of high signal-to-noise ratio ECG signals and surface EMG signals (Figure 6B).[166] To address the issue of excessive sweating, permeable electronics have garnered increasing research attention. A recent study proposed a universal strategy for breathable wearable electronics. The authors

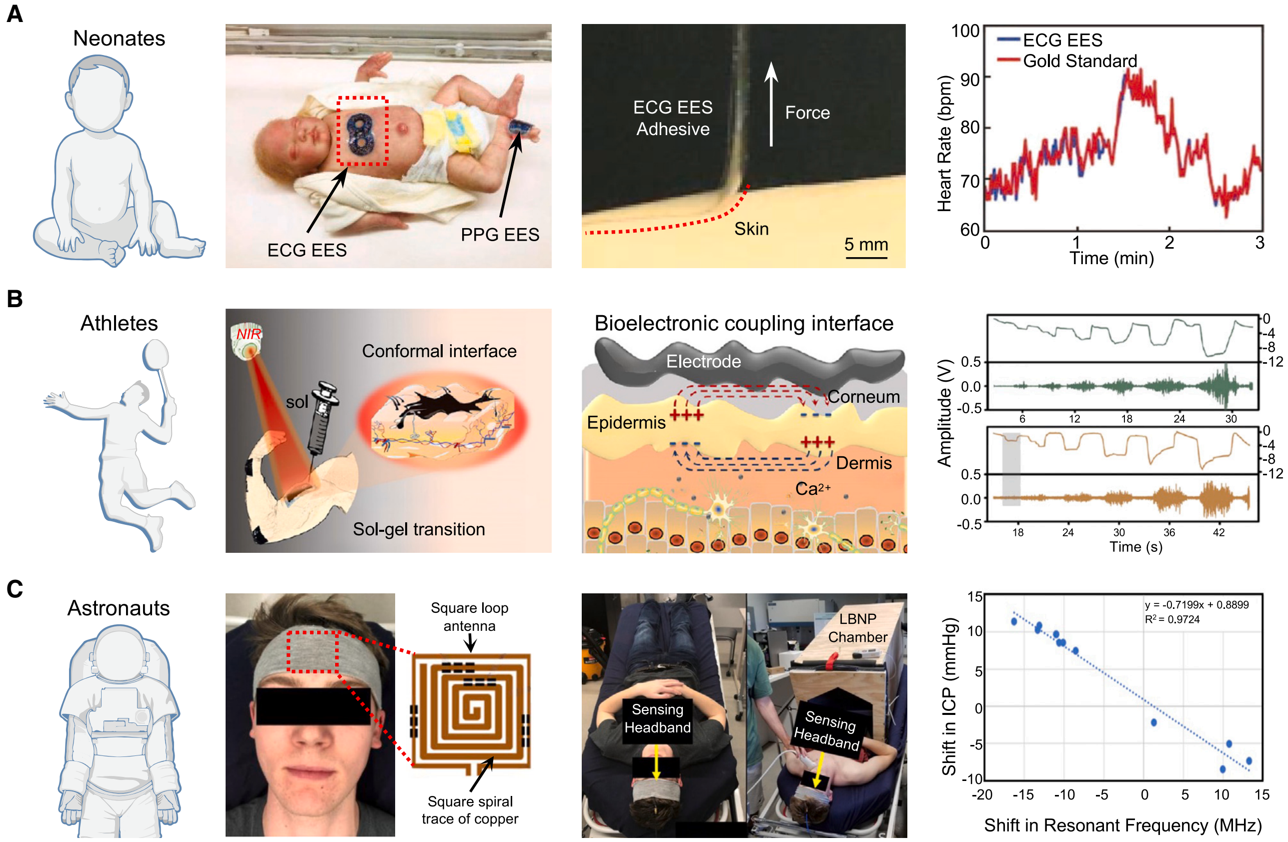

Figure 6. Multimodal bioelectronics for health management of special populations

(A) Bioelectronics for neonatal care with optical images of ECG and photoplethysmogram epidermal electronic system (PPG EES), and demonstration of non-damaging adhesion and detection signals.

(B) Bioelectronics for athlete healthcare with the illustration of *in situ* hydrogel electronics on highly conformal interfaces and the collected sEMG signals compared with commercial electronics.

(C) Bioelectronics for astronaut health monitoring with electromagnetic skin patch to detect intracranial fluid changes in lower body negative pressure (LBNP) experiments.

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constructed spatially heterogeneous wettability, enabling a three-dimensional liquid diode to pump sweat away from the skin at a high flow rate. This design ensures comfortable and stable detection of physiological information under sweating conditions.[167] Apart from daily monitoring, injury prevention is vital for high-intensity athletes. Motion monitoring systems are designed for musculoskeletal junctions and other injury-prone areas, achieving real-time warnings of the risky actions and wrong postures.[168] Additionally, electroactive and self-healable hydrogels integrated with treatment techniques such as electricity stimulation, could accelerate the wound healing procedure.[169]

Astronauts

In the aerospace environment, changes in gravity and atmospheric conditions present unprecedented challenges for humans. In microgravity, alterations in pressure gradients cause biofluids to shift from the lower body toward the head, leading to increased intracranial pressure and disrupting cardiovascular regulation. Conversely, in hypergravity conditions, fluids rapidly redistribute from the head to the lower body, resulting in intracranial hypotension. Non-invasive devices for detecting and quantifying biofluid displacement are essential during ground training and space missions. Related studies have utilized electromagnetic resonant sensors to non-invasively detect intracranial fluid volume. In lower body negative pressure experiments, electromagnetic resonant skin patch sensors detect the intracranial fluid changes during a 15° head-down tilt, where the resonant frequency shifts in response to intracranial volume changes. Figure 6C illustrates the sensor design, experimental setup, and validation of the correlation between resonant frequency and intracranial pressure.[170] Additionally, applications such as detecting and counteracting exoskeleton-induced body pressure[171] and real-time psychological stress[172] are vital for astronaut health and aerospace endeavors. Other populations with specific care needs, such as the elderly and pregnant women, as well as high-risk occupational groups like firefighters and miners, require tailored multimodal bioelectronic solutions. These technologies can play a critical role in injury prevention and vital signal monitoring, enhancing quality of life or improving workplace safety.

PATIENT-CENTRIC HEALTH MANAGEMENT

Accessible medical resources are challenging for patients, especially those suffering from chronic and severe diseases. The treatment process can span decades, occupying a large part of their lives. Beyond frequent hospital visits, many patients are willing to use at-home devices to monitor their health conditions. For example, hypertensive patients use blood pressure monitors, and those with sinus arrhythmia rely on dynamic electrocardiogram devices. However, these specialized devices are typically limited to routine measurements and lack the ability to provide continuous monitoring or alert abnormalities. Even wearable devices like smartwatches fail to extract biofluids and analyze physiological information at molecular levels, necessitating the need for further research and commercialization in this area. This section categorizes common diseases into six sections—skin and respiratory diseases, digestive and cardiovascular diseases, and neurological and mental disorders—to discuss the advancement of patient-oriented multimodal bioelectronics for digital health management.

Skin diseases

Skin diseases encompass a wide range of conditions, including eczema, psoriasis, acne, dermatitis, etc., which significantly affect patients' life quality and impose substantial healthcare burdens globally. Effective and continuous monitoring of skin diseases is essential but still challenging due to the complex nature of skin conditions and the dynamic progression. Wearable bioelectronics can record biophysical signals such as skin impedance, body temperature, and humidity, and also facilitate preliminary treatments like drug release and electrical stimulation. An active bio-integrated living electronics (ABLE) platform has been built to alleviate the symptoms of psoriasis-like skin conditions by modulating the immune environment through microbiota regulation (Figure 7A).[16] The active hydrogel interface supports bacterial viability while ensuring biosafety by electrical stimulation. In addition, the top discomfort caused by atopic dermatitis (AD) is itching, which is not only a symptom but also a driving factor of the disease. Traditional itch measurement relies on subjective reports, lacking accuracy and applicability for children and cognitively impaired individuals. Video observation is accurate but time-consuming, and wrist actigraphy struggles to distinguish scratching from other movements. In such cases, current methods are impractical for clinical trials and daily care. In contrast, the ABLE platform utilizing scratching-related physical signals as a quantitative measurement of itch severity provides a novel perspective for monitoring and assessing AD. In Figure 7B, the advanced acousto-mechanic sensor can capture both low-frequency and high-frequency signals without interference through motion and acousto-mechanical signals. With deep learning algorithms, the system can accurately classify and quantify scratching behavior to objectively measure itch intensity for the evaluation of treatment effectiveness.[127] In addition, early symptoms of acne can be detected through an all-in-one adhesive hydrogel with real-time collection and analysis of the fluids from skin moisture.[128] The electrical field generated by wearable nanogenerators can be utilized to induce fibroblast migration, proliferation, and differentiation, serving as an electronic bandage to promote skin wound healing.[129] A multi-component drug-loaded electronic microneedle system, with the synergistic effect of energy harvesting module, enables efficient cellular penetration and specific immune modulation for the treatment of inflammatory skin diseases.[130,131] The implementation of multifunctional bioelectronics has advanced the routine detection and treatment of skin diseases.

Respiratory diseases

Respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis, pose significant threats to public health due to their high prevalence and potential for severe complications. These conditions can severely impair lung function, leading to considerable morbidity and mortality worldwide. Traditional medical examinations, typically conducted at specific times, fail to provide continuous data. However, respiratory diseases often exhibit sporadic or intermittent symptoms, which may be undetectable by conventional diagnostic methods with delayed treatment. For example, common methods for detecting respiratory diseases include gas sensors for detecting volatile organic compounds (VOCs)[173] and throat sensors for detecting facial and neck muscle movements.[135] Advanced bioelectronic technology like utilizing exhaled breath condensate (EBC) have shown promising prospects for non-invasive respiratory disease monitoring. Wearable devices covering the face (or mouth) designed for sampling and *in situ* analysis should overcome challenges such as active vapor condensation, efficient liquid collection, and waste disposal. A representative example achieves active vapor condensation through hydrogel evaporative cooling, radiative cooling, and frameworks made of high thermal conductivity materials. Due to its high water content and the temperature difference, the cooling hydrogel positioned on the outer side of the mask can achieve a cooling effect of 8°C in standard indoor environments. However, to maintain sustainable and stable cooling performance, continuous liquid replenishment is highly required at the same time. Liquid collection is enhanced by surface hydrophilicity and a micro-gradient pillar array that strengthens capillary action. Additionally, cooling hydrogels can absorb waste liquid, enabling continuous circulation within the microsystem. As shown in Figure 7C, this device is suitable for the continuous monitoring of EBC biomarker concentrations in patients with COPD.[136] From the perspective of sensing performance, acute and severe respiratory diseases such as asthma demand high sensitivity and fast response time from humidity sensors, while the cumulative effects of continuous monitoring would impact signal accuracy. Humidity sensors with a response time of less than 20 ms can accurately capture the depth and frequency of breathing during asthma episodes (Figure 7D).[137] Due to the influence of environmental factors and gas instability, it is critical to detect respiratory diseases with efficient biomarker collection, real-time monitoring, and early warning systems. Since the worldwide coronavirus disease in 2019, the mask has been recognized as a personal protective measurement. A pathogenic infection diagnosis system has realized virus infection diagnosis

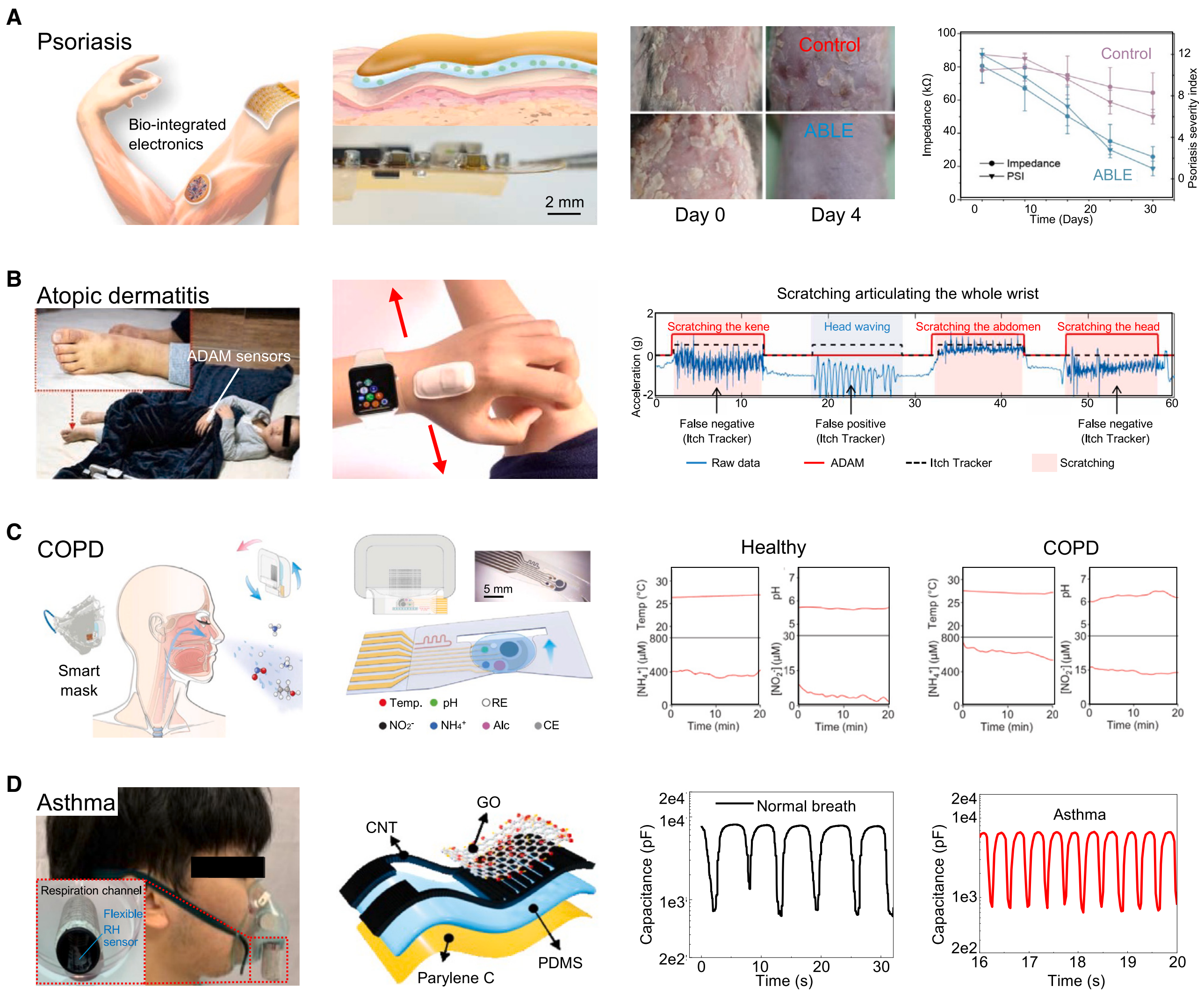

Figure 7. Multimodal bioelectronics for skin and respiratory diseases

(A) Active bio-integrated living electronics platforms intervene in psoriasis by modulating the immune environment through microbiota regulation.
(B) Advanced acousto-mechanic (ADAM) sensor quantitatively measures itch severity to monitor and assess atopic dermatitis.
(C) Exhaled breath condensate (EBC) analysis and respiratory evaluation for EBC biomarker levels of healthy individuals and people with COPD.
(D) A flexible humidity sensor with an ultrafast response of ~20 ms to accurately capture the depth and frequency of breathing during asthma episodes.
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by breath and blow. By gaseous sample collection, biomarker identification, physical signs recording, and ML analysis, the system can rapidly diagnose SARS-CoV-2 infection and precisely recognize symptom severity.[138] In addition to gas sensing, masks integrated with a soundwave sensor can record various respiratory sounds or activities for daily monitoring of symptoms like cough.[139] Smart masks with innovative functions are meaningful for respiratory infectious disease prevention and public health.

Digestive system diseases

Digestive system diseases, including inappetence, anastomotic leaks, irritable bowel syndrome, gastric ulcers, and colorectal cancer, are highly associated with gastrointestinal functions and overall health, leading to chronic pain and malnutrition. Common ways for monitoring and diagnosis are invasive, where biocompatibility is of paramount importance with two categories, bioresorbable and completely inert. For instance, the implantable metal disks utilize bioresorbable metals and hydrogel materials, which experience dissolution reactions and hydrolytic chain scission in biofluids. After surgery, these polymer hydrogel-based metal disks could be sutured near anastomosis sites to detect anastomotic leaks by ultrasound enhancement (Figure 8A).[143] Due to the invisibility and uncertainty of gastric lesion locations, internal devices often require coordination with external equipment. Besides implantable configuration,

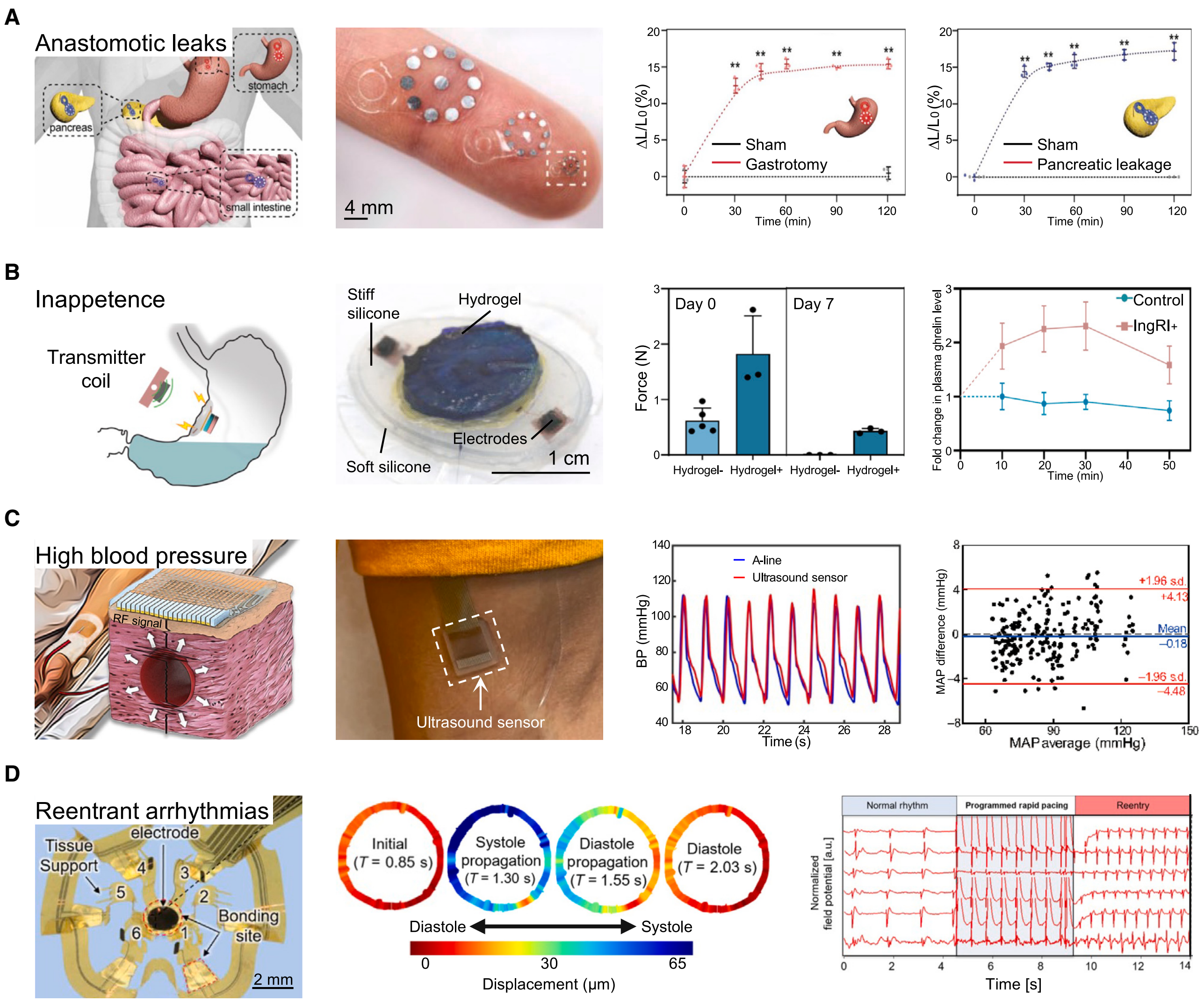

Figure 8. Multimodal bioelectronics for digestive system and cardiovascular diseases

(A) Bioresorbable metal disks could enhance postoperative ultrasound contrast for anastomotic leaks detection.

(B) An ingestible, battery-free, and tissue-adhering robotic interface allowing electrical stimulation to alleviate inappetence.

(C) A redesigned ultrasound sensor to achieve full arterial coverage and offer substantial tolerance for device–artery misalignment, realizing exceptional accuracy in blood pressure measurement.

(D) 3D multifunctional mesoscale frameworks designed for heart tissue patches to accurately detect the rhythm of cardiac contraction and relaxation.

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recent studies have reported a non-invasive electronic device that can be introduced through the esophagus to achieve stable tissue contact. Once placed, it can be remotely positioned using an external magnet (Figure 8B). Furthermore, utilizing near-field inductive coupling, the device enables programmable electrical pulse output to stimulate the stomach with alleviated inappetence.[144] A deformable electronic esophageal stent has been built for wireless stimulation of the lower esophageal sphincter, offering a novel treatment approach for gastroesophageal reflux disease.[142] In addition to implantable bioelectronics, wearable devices could monitor gastrointestinal muscle activity for patients with chronic gastric conditions. It is ideal to monitor circadian rhythm for gastric electrical activity but limited by in-patient department testing. The developed gastric array patches, along with automated computational methods, can provide results that align with the gold standard for gastrointestinal motility assessment.[141]

Cardiovascular diseases

According to the World Health Organization, cardiovascular diseases are the leading cause of death worldwide, such as high blood pressure, reentrant arrhythmias, and atherosclerosis. For individuals at high risk of cardiovascular diseases, in addition to using portable devices such as blood pressure monitors, heart rate monitors, and pulse oximeters, commercial tests like ECG and blood tests still require frequent hospital visits. Research by American scholars has demonstrated that, after adjusting for traditional risk factors, abnormalities in ECGs are associated with an elevated risk of subsequent cardiovascular events,[174] emphasizing the importance of long-term monitoring. Currently, a growing amount of research is dedicated to achieving precise and long-term ECG monitoring. Utilizing ultrasound for vascular blood pressure monitoring at the epidermal level holds promise for improving patient care. Wearable ultrasound sensors have been implemented to meet clinical standards. The redesigned ultrasound sensor incorporates closely connected sonographic windows and a backing layer, addressing the challenges of achieving full arterial coverage and offering substantial tolerance for device–artery misalignment.[150] As shown in Figure 8C, the ultrasound sensor demonstrates exceptional accuracy in blood pressure measurement. In addition, body fluids also contain rich information to reflect cardiovascular health. For complex diseases like atherosclerosis, multimodal monitoring of multiple biomarkers such as cholesterol, transferrin, and K^+ facilitates personalized and standardized assessment.[175] In addition to the continuous monitoring of wearable bioelectronics, implantable bioelectronics used in surgeries also demonstrate impressive improvements. For a damaged heart, engineered heart tissue patches (EHTs) can form cardiomyocytes with scaffold materials, which are bioengineered materials constructed by combining seed cells. Despite the rapid advancements in the theoretical research of EHTs, numerous challenges remain in their clinical applications. In 2016, nanoscale electronic scaffold structures were introduced into EHTs, enabling seamless integration and real-time monitoring of the electrophysiological signals of myocardial tissue, enabling dynamic tracking of transient arrhythmia disease and subsequent tissue self-adaptation. Furthermore, 3D multifunctional mesoscale frameworks (3DMMFs) designed for EHTs can deliver specific electrical stimulation through different electrodes (Figure 8D). The electrophysiological signals on ring-shaped 3DMMFs demonstrate reentrant rhythms, offering potential for simulating human cardiac arrhythmias.[151]

Neurological disorders

Neurological disorders are a leading cause of poor health and disability, with high prevalence rate of diseases, such as stroke, epilepsy, Alzheimer's disease, and Parkinson's disease. Analyzing EEGs or neurotransmitter data is critical for diagnosing and treating neurological disorders. In the brain, immune rejection reactions, such as inflammation-mediated gliosis, can be permanently damaging. The next generation of neural interfaces aims to achieve superior biocompatibility while ensuring efficient signal recording. Using silk fibroin with excellent biocompatibility to establish efficient and safe neural interfaces is a potential approach.[157] Additionally, interfaces designed by thermal-assisted pattern-transfer technology enable cortical electroencephalogram (ECoG) recording and inflammation mitigation in rats. Figure 9A illustrates the application of this neural interface in monitoring epilepsy. A neural chemical-biological interface called NeuroString supports long-term monoamine sensing in the brain of mice and the measurement of serotonin dynamics in the gut. This bioelectronic device is fabricated by laser patterning metal-complexed polyimide into interconnected graphene-nanoparticle networks embedded within an elastomer. Figure 9B demonstrates the concentration-dependent responses of NeuroString electrodes to dopamine and serotonin.[152] Flexible brain–computer interfaces represent a revolution in neuroscience. Notably, interface design needs to achieve the balance of mechanical properties and conformality with brain tissue. It is expected to realize the technologies capable of precisely activating or inhibiting specific types of neurons, thus enabling personalized diagnosis and treatment.[176]

Mental disorders

Mental disorders arise from brain dysfunction, leading to varying degrees of impairment in cognitive, emotional, volitional, and behavioral activities. In addition to physiological factors, stress can affect the brain and psyche through the immune system.[177] With increasing societal pressures, promoting recognition of emotions and monitoring of stress levels is essential for early prevention of conditions such as depression and anxiety. Traditional medical approaches for diagnosing mental disorders or assessing anxiety levels often rely on standardized questionnaires and scales. Whether self-reported by patients or evaluated by professionals based on patient behavior, these methods are time-consuming and inherently subjective. Physical examinations and blood sampling used in diagnosing somatic conditions may further exacerbate patient anxiety. In contrast, wearable bioelectronics offer a promising alternative by enabling continuous monitoring of disease-specific biomarkers. For instance, measurement of cortisol levels in sweat has emerged as a simple and effective method for stress assessment. The related study shows a strong correlation of cortisol levels in sweat, serum, and saliva. Utilizing the electrochemical properties of laser-induced graphene, a flexible sensor array enables selective detection of cortisol in sweat, providing cortisol diurnal cycle and the dynamic stress-response profile for stress-related disorder diagnosis.[15] Since cortisol is unable to provide comprehensive understanding for mental stress, accurate assessment of mental health requires the integration of multiple biomarkers, EEG signals, and other indicators. Among them, it is critical to analyze EEG signals for emotion recognition and classification. In addition to sensing design, signal recognition and classification heavily rely on processors and advanced algorithms. For instance, in portable headbands equipped with integrated data processing modules, an adhesive and hydrophobic bilayer hydrogel paired with a neural network achieves remarkably high classification accuracy of EEG-based emotion recognition in medical monitoring (Figure 9C).[159] Multimodal monitoring is vital for conditions that manifest both physiologically and psychologically. A consolidated artificial-intelligence-reinforced electronic skin was reported, achieving long-term continuous monitoring and precise assessment of stress. As shown in Figure 9D, the physicochemical sensor data, including three vital signs and six sweat molecular biomarkers, in coordination with advanced ML, realizes high-precision classification of responses to stressors and prediction of anxiety levels.[11]

Interface construction, multimodal sensing, and data processing have enabled bioelectronics for diagnosis and monitoring of most diseases. In terms of non-invasive bioelectronics, accurate

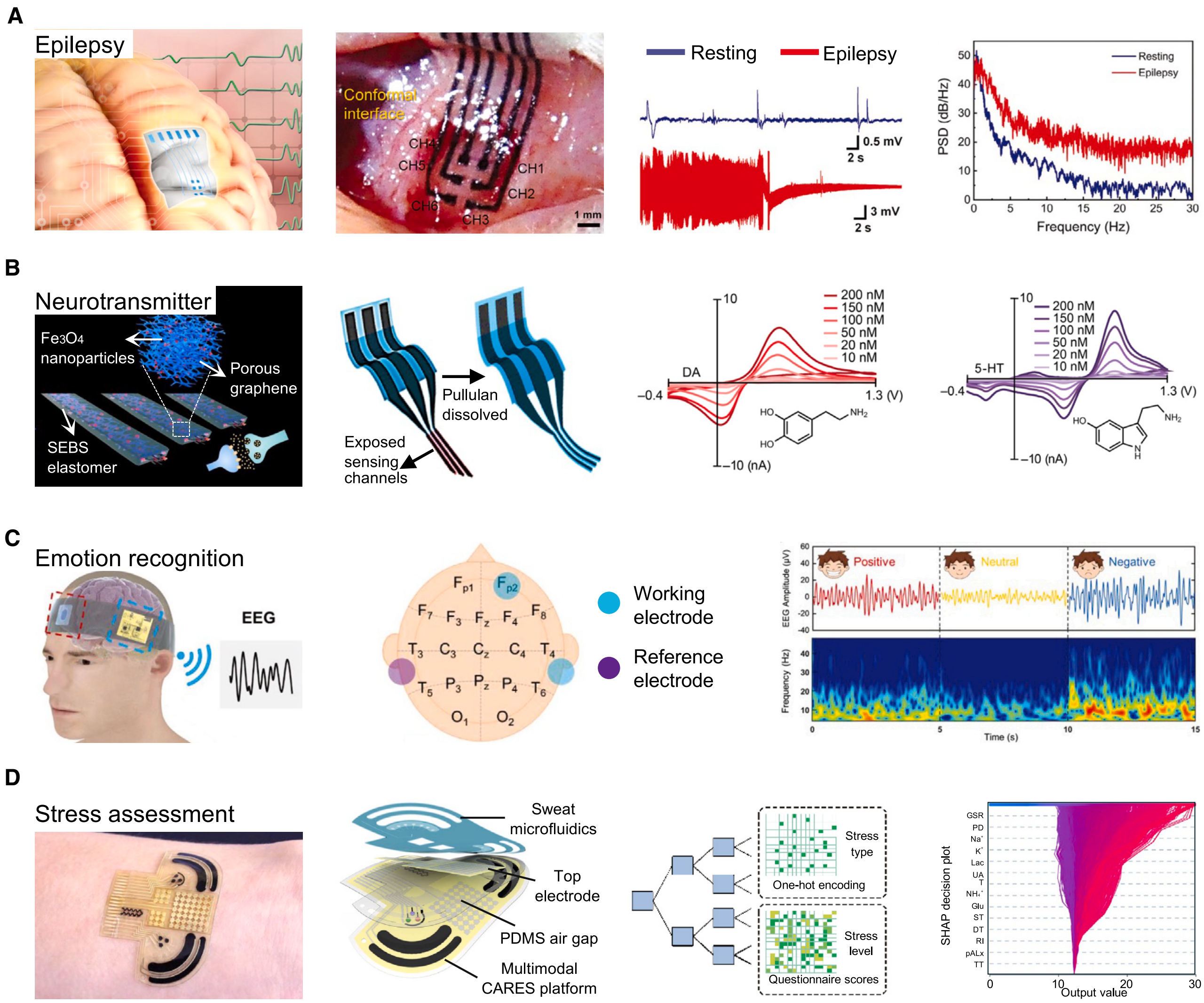

Figure 9. Multimodal bioelectronics for neurological system diseases and mental disorders
(A) Silk fibroin-based biocompatible neural interface to monitor epilepsy through electroencephalogram signals.
(B) The schematic diagram of NeuroString with the concentration-dependent responses to dopamine and serotonin.
(C) A portable headband showing high classification accuracy with the transfer learning technique-based neural network.
(D) A consolidated artificial-intelligence-reinforced electronic skin with high-precision classification of stressor types and prediction of stress levels.
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acquisition of biophysical signals is essential for comprehensive physiological assessment. For example, gas sensors can detect harmful or abnormal gases to protect human health. A platform achieves detection and quantification of NO_2 exposure and respiratory anomalies by exploiting the physicochemical properties of $Ti_3C_2Tx@Cu_3(HHTP)_2$, with their enhanced material interfacial interactions and large surface area.[178] Acoustic sensors can recognize speech for individuals with vocal disorders. The liquid acoustic sensor based on a permanent fluidic magnet features self-filtering capabilities and offers a recognition accuracy of 99% in noisy environments.[179] Temperature sensors can locate inflamed or diseased skin, where an amorphous silicon-based temperature sensor array combined with drug-loaded hydrogels can precisely capture inflammation-induced temperature changes and enable heat-triggered drug release.[180]

For the monitoring of biochemical signals, diverse biofluids are available for wearable bioelectronics, such as sweat, tears, saliva, and urine. For sweat sensors, which are most frequently studied, an integrated platform with fluid extraction, collection, and evaluation is indispensable. Methods like electrical-stimulated sweating for fluid sampling are increasingly noticed, as well as microfluidics technologies and specific biomarker sensing capabilities to realize continuous health monitoring.[181] Key biomarkers in tears include vitamin C, H^+, Ca^{2+}, and proteins. A wearable microfluidic colorimetric sensor system was proposed for rapid and simultaneous tear detection by the colorimetric reaction and deep learning data analysis system for eye health.[182] Saliva testing is closely linked to oral health. A portable saliva biosensor designed for the early detection of *Streptococcus mutans* employs aptamer/bacteria-imprinted polymer non-enzymatic dual-recognition elements for the prediction of dental cavities.[183] The urine detection methods including monitoring of symmetric dimethylarginine, and creatinine and albumin for kidney dysfunction, have been investigated, remaining to be integrated with wearable system designs.[184,185]

For electrophysiological signals such as ECG, EMG, and electrodermal activity (EDA), it is essential to amplify weak, low-frequency signals and minimize interference. The latest epidermal fiber electrodes have achieved imperceptible collection of ECG and EMG signals at the fingertips. The substrate-free and open fiber networks based on poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) achieve imperceptible augmentation of living systems through *in situ* tethering, enabling stable monitoring of electrical signals.[186] EDA serves as the quantitative indicator of mental stress, demonstrating significant utility across diverse neuroergonomic investigations. The challenges of EDA monitoring lie in obstructiveness or low signal fidelity, while advanced heterogeneous serpentine ribbons incorporating graphene-based e-tattoos facilitate continuous, high-resolution EDA monitoring of palmar under free-living conditions.[187]

As for implantable bioelectronics, given the invasive nature, it requires a shift toward minimally invasive designs with long-term usability. Commercial implantable bioelectronics like Programmable Neurostimulator for Gastric Electrical Stimulation (Medtronic), are designed for long-term use, often lasting for years. In addition, the battery-free, tissue-adhering robotic interface has demonstrated the ability to deliver programmable electrical pulses via near-field inductive coupling at 13.56 MHz for 48 h.[144] In a recent study, a sensing electrode ribbon capable of wirelessly transmitting bioelectric signals, such as gastric slow waves, successfully monitored stomach activity for 4 days.[145] However, developing bioelectronics that can be implanted for over a month remains a significant challenge, necessitating advances in biocompatibility, electrical performance, and mechanical robustness.[188] For example, in the design of direct-contact cardiac electrode arrays, the vigorous beating of the heart often causes electrode detachment and coating voltage-sensitive dyes for optical mapping introduces unavoidable biotoxicity. In this context, utilizing intrinsically stretchable conductive polymers as electrode materials to microfabricate high-density electrode arrays can acquire clear and reliable ECG signals, advancing the research and treatment of atrial fibrillation.[189]

CHALLENGES AND OUTLOOK

The rapid advancements in bioelectronics have revolutionized medical healthcare by accurate diagnosis, continuous monitoring, and personalized treatment. This review adopts a bottom-up approach, covering advanced materials, interface designs, system integration, special population health management, and practical applications toward specific diseases (Figure 10).

While emerging devices have rapidly innovated in sensitivity, instant response, and multifunctionality, multimodal bioelectronics still faces challenges regarding advanced materials design, long-term device durability, efficient fabrication, and system integration. First, the mismatch of Young's modulus between multilayered materials compromises device flexibility and conformability, and differences in thermal expansion coefficients induce stress disparities. For devices involving multiple material components, the compatibility of physicochemical properties is paramount for optimal performance. Second, device stability remains a widespread concern due to complex fabrication processes and variable environmental factors. For mechanical strength, brittle thin films on flexible substrates tend to crack and propagate during deformation. The optimization of molecular structure design for mechanical-robust flexible substrates should be emphasized. For interface adhesion, slippage, delamination, and hardening of bonding layers are common problems for conformability and sensing performance.[190] They can be mitigated through various interface engineering strategies, including surface modification and adhesive enhancement. Furthermore, comprehensive long-term fatigue tests of devices are essential, along with the establishment of standardized stability assessment. Third, fabrication methods require further optimization. Techniques like photolithography often introduce solvent residues, creating defects that impair electrical performance. Common printing methods, such as roll-to-roll and transfer printing, frequently fail due to insufficient adhesion between printed materials and the substrate, leading to uneven circuits. Emerging manufacturing techniques such as direct-ink-writing 3D printing, laser direct structuring, and hybrid manufacturing should be involved to enhance production efficiency and device consistency. Last, electrochemical failures are increasingly observed in flexible energy storage devices, where electrode materials degrade under deformation with the risk of device breakdown.[191,192] To resolve failure modes at different usage stages, researchers need to investigate the underlying failure mechanisms to identify effective solutions. A comprehensive and standardized testing framework should be established to evaluate the requirements for wearable and implantable bioelectronics.

Multimodal bioelectronics has brought exciting opportunities to human health by multiple sensing components including biophysical, biochemical, and bioelectrical sensors. To fully realize the potential of these technologies, the development of multimodal bioelectronics should transition from basic applications to more complex and personalized systems. First, due to the intricate structure of biological systems, most diseases exhibit complex etiologies, requiring coordinated detection of multiple physiological information through multimodal sensing approaches. For instance, in the case of female hormone disorders such as polycystic ovary syndrome, simultaneous monitoring of skin temperature, sweat pH, estradiol levels, and ion concentrations ensures the accuracy of abnormality analysis.[193] Meanwhile, it is critical to analyze and process the multimodal data with the involvement of ML. For example, systems with the integrated image–language model for diabetes diagnosis and management enhance the optimization of multimodal data fusion, provide auxiliary diagnostic results, and offer personalized diabetes management recommendations.[194] Second, multimodal bioelectronics should evolve beyond diagnosis and continuous

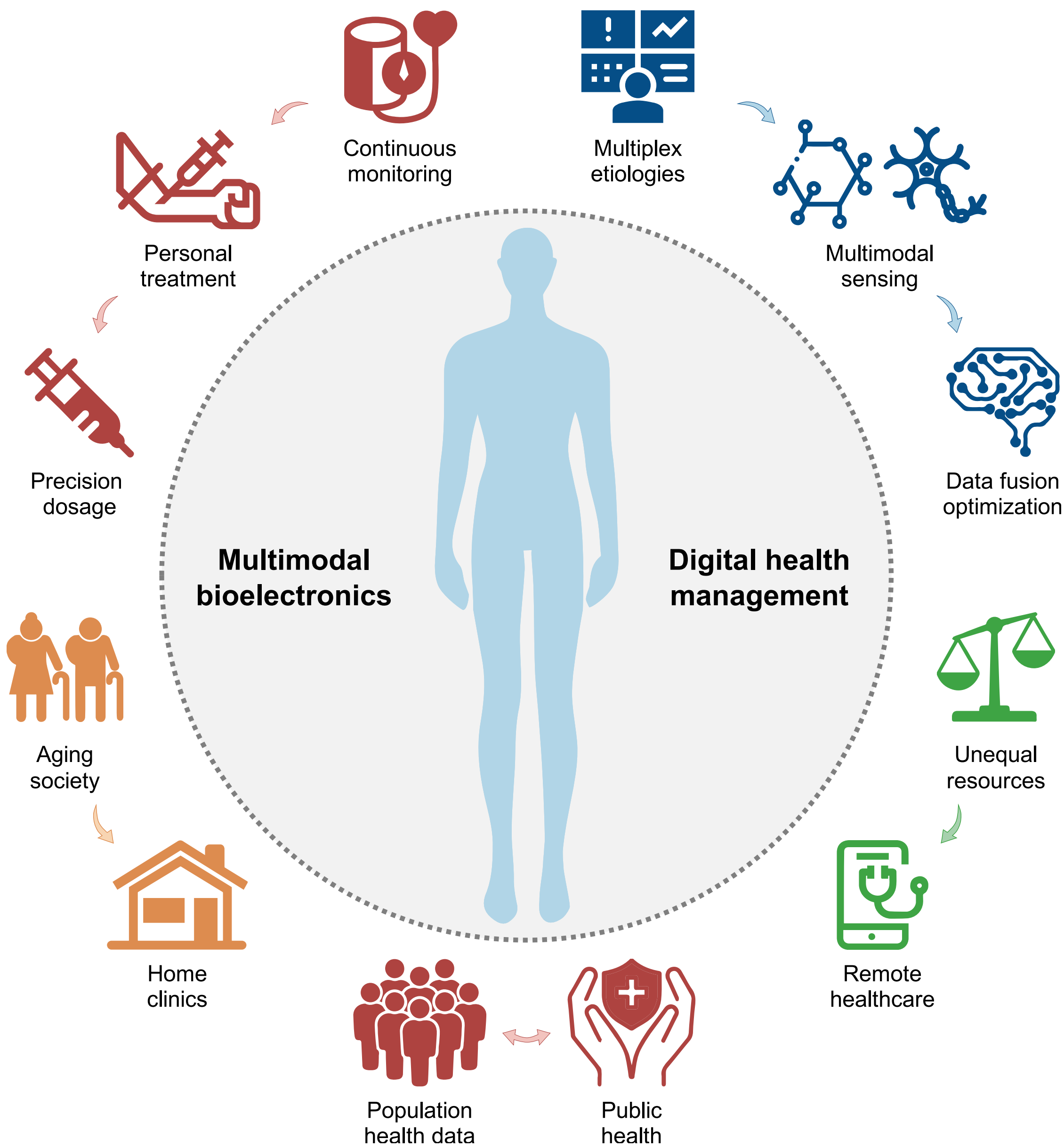

Figure 10. Challenges and outlook of multimodal bioelectronics for digital health management

monitoring to therapeutic functions. Current therapeutic approaches include subcutaneous microneedle drug delivery and electrical stimulation. However, treatment modalities that align with clinical applications remain underdeveloped. Notably, precise drug delivery systems are intrinsically linked to therapeutic capabilities, necessitating substantial research endeavors. Third, digital health should evolve from an individual perspective to a population-based statistical concept. With the progression of global aging, the concept of home clinics is gaining attention and multimodal bioelectronics can play a critical role in this context. In regions with limited medical resources and a shortage of healthcare personnel, telemedicine improves in parallel with economic development, serving as a key factor for the widespread adoption of digital health. Furthermore, the integration of population health data can provide valuable insights into public health trends and disease prevention strategies. To this end, bioelectronics is required to establish data platforms in the era of connectivity, coupled with secure management of sensitive information.

In summary, multimodal bioelectronics inherently integrates multidiscipline such as chemistry, physics, materials science, and biomedical engineering, bridging the gap between the medical challenges for healthcare professionals and the engineering problems for biomedical researchers. Bioelectronics for digital health is revolutionizing healthcare by enhancing health data acquisition and improving patient outcomes. This transformative technology is anticipated to foster societal well-being and hold the promise of shaping a more connected and healthier future for the whole world.

ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of Guangdong Province, China (2025A1515010362); the City University of Hong Kong (grant no. 9382003); the University Grants Committee's Teaching Start-up Grant (CityUHK grant no. 6000908); the National Natural Science Foundation of China (grant no. T2225017); and the Science Technology and Innovation Committee of Shenzhen Municipality (grant no. JCYJ20241202125402004).

AUTHOR CONTRIBUTIONS

Conceptualization, Y.S.; investigation, M.G.; writing – original draft, M.G.; writing – review & editing, Y.S. and C.F.G.; supervision, Y.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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