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Special Issue Reprint

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# Wearable and Implantable Electrochemical Sensors

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Edited by  
Zhanhong Li, Zhigang Zhu, Zifeng Wang and Nan Zhu

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# **Wearable and Implantable Electrochemical Sensors**



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Guest Editors

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# Contents

|                                                                                                                                                                                                                                                                                                   |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| About the Editors . . . . .                                                                                                                                                                                                                                                                       | vii |
| Preface . . . . .                                                                                                                                                                                                                                                                                 | ix  |
| <b>Emanuele Raso, Francesca Nanni, Francesco Lestini, Lorenzo Bracciale, Giorgia Panico, Giuseppe Bianchi, et al.</b>                                                                                                                                                                             |     |
| Improving Vulnerability Management for Security-by-Design of Medical Devices<br>Reprinted from: <i>Sensors</i> <b>2025</b> , 25, 4418, <a href="https://doi.org/10.3390/s25144418">https://doi.org/10.3390/s25144418</a> . . . . .                                                                | 1   |
| <b>Muhammad Sheraz, Xiao-Feng Sun, Adeena Siddiqui, Yongke Wang, Sihai Hu and Ran Sun</b>                                                                                                                                                                                                         |     |
| Cellulose-Based Electrochemical Sensors<br>Reprinted from: <i>Sensors</i> <b>2025</b> , 25, 645, <a href="https://doi.org/10.3390/s25030645">https://doi.org/10.3390/s25030645</a> . . . . .                                                                                                      | 18  |
| <b>Yao Chu, Zhengzhong LvZeng, Kaijie Lu, Yangyang Chen, Yichuan Shen, Kejia Jing, et al.</b>                                                                                                                                                                                                     |     |
| Magnetic Porous Hydrogel-Enhanced Wearable Patch Sensor for Sweat Zinc Ion Monitoring<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 5627, <a href="https://doi.org/10.3390/s24175627">https://doi.org/10.3390/s24175627</a> . . . . .                                                       | 37  |
| <b>Zeyi Tang, Jinming Jian, Mingxin Guo, Shangjian Liu, Shourui Ji, Yilong Li, et al.</b>                                                                                                                                                                                                         |     |
| All-Fiber Flexible Electrochemical Sensor for Wearable Glucose Monitoring<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 4580, <a href="https://doi.org/10.3390/s24144580">https://doi.org/10.3390/s24144580</a> . . . . .                                                                   | 47  |
| <b>Fangfang Luo, Zhanhong Li, Yiping Shi, Wen Sun, Yuwei Wang, Jianchao Sun, et al.</b>                                                                                                                                                                                                           |     |
| Integration of Hollow Microneedle Arrays with Jellyfish-Shaped Electrochemical Sensor for the Detection of Biomarkers in Interstitial Fluid<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 3729, <a href="https://doi.org/10.3390/s24123729">https://doi.org/10.3390/s24123729</a> . . . . . | 58  |
| <b>Yuxin Wan, Caiyi Wang, Bingao Zhang, Yixuan Liu, Hailong Yang, Fengyu Liu, et al.</b>                                                                                                                                                                                                          |     |
| Biocompatible Electrical and Optical Interfaces for Implantable Sensors and Devices<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 3799, <a href="https://doi.org/10.3390/s24123799">https://doi.org/10.3390/s24123799</a> . . . . .                                                         | 72  |
| <b>Meiqing Jin, Peizheng Shi, Zhuang Sun, Ningbin Zhao, Mingjiao Shi, Mengfan Wu, et al.</b>                                                                                                                                                                                                      |     |
| Advancements in Polymer-Assisted Layer-by-Layer Fabrication of Wearable Sensors for Health Monitoring<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 2903, <a href="https://doi.org/10.3390/s24092903">https://doi.org/10.3390/s24092903</a> . . . . .                                       | 84  |
| <b>Jialin Liu, Yitao Wang, Yiwei Liu, Yuanzhao Wu, Baoru Bian, Jie Shang and Runwei Li</b>                                                                                                                                                                                                        |     |
| Recent Progress in Wearable Near-Sensor and In-Sensor Intelligent Perception Systems<br>Reprinted from: <i>Sensors</i> <b>2024</b> , 24, 2180, <a href="https://doi.org/10.3390/s24072180">https://doi.org/10.3390/s24072180</a> . . . . .                                                        | 116 |



# About the Editors

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Zhanhong Li is an Associate Professor at the School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, China. He is dedicated to the development of wearable and implantable electrochemical sensing technologies for continuous health monitoring and personalized medicine. His primary research interests include wearable biosensors, microneedle-based electrochemical sensors, bioelectronic interfaces, flexible electronics, and minimally invasive biochemical sensing. His work integrates electrochemistry, functional materials, microfabrication, and biomedical engineering to develop intelligent sensing platforms for the real-time analysis of biomarkers in biofluids. He has contributed to the design and development of wearable sensing devices with applications in healthcare monitoring, disease diagnosis, and digital medicine. He also serves as a Guest Editor for international Special Issues in the fields of electrochemical sensing and biosensors, promoting interdisciplinary collaboration in wearable sensing technologies and biomedical engineering.

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Zifeng Wang is a faculty member at the School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, China, where he joined in 2021. His research focuses on flexible multifunctional wearable sensors for healthcare monitoring and intelligent human-machine interaction. His primary research interests include flexible gas sensors, electrochemical sensors, electromechanical sensors, soft electronics, and micro- and nano-fabrication technologies. He is dedicated to integrating advanced functional materials with scalable fabrication strategies to develop mechanically compliant, environmentally friendly, and multifunctional sensing devices for applications in personalized healthcare, motion monitoring, and soft robotics. His research also explores flexible sensor integration, signal acquisition, and intelligent sensing systems

for next-generation wearable electronics. He has contributed to the development of wearable sensing technologies through research on flexible electronic devices, advanced functional materials, and intelligent sensing systems and has published widely in the fields of materials science, flexible electronics, and biosensors.

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# Preface

Wearable and implantable electrochemical sensors have become one of the most dynamic research areas in analytical science, biomedical engineering, and personalized healthcare. By enabling continuous and minimally invasive monitoring of biochemical information in bodily fluids, these sensing technologies are reshaping approaches to disease diagnosis, health management, and precision medicine. Rapid advances in functional materials, flexible electronics, microfabrication, wireless communication, artificial intelligence, and system integration have further accelerated the development of highly sensitive, reliable, and user-friendly sensing platforms.

This Reprint brings together representative contributions from the Special Issue Wearable and Implantable Electrochemical Sensors, providing an overview of recent progress in this rapidly evolving field. The collected papers span fundamental studies and practical applications, covering topics including sensor materials and device design, fabrication strategies, biointerfaces, electrochemical detection mechanisms, signal processing, data analysis, and emerging applications for the monitoring of biomarkers in blood, interstitial fluid, sweat, and other biological media. Together, these contributions highlight both technological innovations and the multidisciplinary collaborations that continue to drive the field forward.

The motivation for compiling this Reprint is to provide researchers with a coherent collection of high-quality studies that reflect current achievements while identifying remaining scientific and engineering challenges. Although remarkable progress has been made, further advances in long term stability, biocompatibility, selectivity, power management, data interpretation, manufacturing scalability, and clinical translation remain essential for widespread practical implementation. By presenting diverse perspectives from leading researchers, this Reprint aims to stimulate new ideas, encourage interdisciplinary collaboration, and inspire future innovations in wearable and implantable electrochemical sensing technologies.

This Reprint is intended for researchers, engineers, clinicians, graduate students, and professionals working in electrochemical sensing, biosensors, wearable electronics, biomedical engineering, materials science, analytical chemistry, and digital healthcare. We hope that it will serve not only as a valuable reference for current developments but also as a source of inspiration for future research and technological advances that will ultimately contribute to improved healthcare and quality of life.

**Zhanhong Li, Zhigang Zhu, Zifeng Wang, and Nan Zhu**

*Guest Editors*



## Article

# Improving Vulnerability Management for Security-by-Design of Medical Devices

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**Abstract:** The healthcare industry is witnessing a rapid rise in the adoption of wearable and implantable medical devices, including advanced electrochemical sensors and other smart diagnostic technologies. These devices are increasingly used to enable real-time monitoring of physiological parameters, allowing for faster diagnosis and more personalized care plans. Their growing presence reflects a broader shift toward smart connected healthcare systems aimed at delivering immediate and actionable insights to both patients and medical professionals. At the same time, the healthcare industry is increasingly targeted by cyberattacks, primarily due to the high value of medical information; in addition, the growing integration of ICT technologies into medical devices has introduced new vulnerabilities that were previously absent in this sector. To mitigate these risks, new international guidelines advocate the adoption of best practices for secure software development, emphasizing a *security-by-design* approach in the design and implementation of such devices. However, the vast and fragmented nature of the information required to effectively support these development processes poses a challenge for the numerous stakeholders involved. In this paper, we demonstrate how key features of the Malware Information Sharing Platform (MISP) can be leveraged to systematically collect and structure vulnerability-related information for medical devices. We propose tailored structures, objects, and taxonomies specific to medical devices, facilitating a standardized data representation that enhances the security-by-design development of these devices.

**Keywords:** cybersecurity; medical devices; security-by-design; CTI; MISP

## 1. Introduction

The healthcare industry is witnessing a rapid rise in the adoption of wearable and implantable medical devices, including advanced electrochemical sensors and a wide range of other smart diagnostic technologies. These innovations are increasingly being integrated into next-generation medical systems to enable real-time and continuous monitoring of critical physiological parameters such as glucose levels, heart rate, body temperature, respiration, and even neural activity. Examples include optical sensors for oxygen saturation and blood flow, bioimpedance sensors for hydration and respiratory tracking, electrophysiological sensors such as ECG and EMG for cardiovascular and muscular activity, and piezoelectric sensors for detecting pressure or mechanical strain within tissues.



The utility of these sensors lies not only in their accuracy and miniaturization but also in their compatibility with biocompatible materials that allow for safe long-term use in or on the human body. Their integration into smart and connected platforms—commonly referred to as medical Internet of Things (IoT) devices—marks a paradigm shift toward proactive data-driven healthcare. These systems are capable of generating large volumes of health-related data in real time to support timely diagnoses, early warning systems, personalized treatment plans, and more effective patient follow-up.

Moreover, the ability of these devices to provide remote, high-frequency, and context-aware monitoring enhances the responsiveness of healthcare professionals, enabling more informed and rapid medical decisions. This is particularly crucial in chronic care, post-operative recovery, and emergency medicine. By improving interoperability, safety, and patient engagement, smart wearable and implantable devices are becoming essential components in modern healthcare ecosystems, fostering better communication between patients and clinicians while also supporting the broader goals of preventive medicine and digital health transformation. However, as emphasized in [1], the integration of such connected technologies must be accompanied by robust and well-defined security frameworks, without which the confidentiality, integrity, and availability of sensitive medical data can be compromised. Due to their continuous data collection and wireless communication, medical IoT devices increase the system's attack surfaces, and as such require explicit policy-driven mechanisms to control access, authenticate users, and ensure auditability. All of these principles are critical for protecting both patients and healthcare infrastructure within the evolving digital landscape.

The healthcare sector has recently witnessed a surge in cyberattacks. Between 1 January 2018 and 30 September 2023, the U.S. Department of Health and Human Services Office for Civil Rights reported a 239% increase in hacking-related data breaches and a 278% rise in ransomware incidents [2]. Additionally, 92% of healthcare organizations were affected by cyberattacks in 2024, up from 88% in the previous year [3]. Compromised healthcare information can be up to fifty times more valuable than financial data, with complete medical records fetching as much as USD 1000. According to [4], malware remains the most prevalent attack vector (35%), with exploitation of known vulnerabilities surging from 11% in 2022 to 24% in 2023. This trend underscores the urgent need for enhanced cybersecurity measures and greater preparedness across the healthcare industry.

The research community has responded to these security challenges by developing comprehensive frameworks for securing medical devices, including recent work on secure IoT implementations for healthcare applications [5].

Modern Implantable Medical Devices (IMDs) introduce additional security concerns due to their wireless capabilities [6,7]. Threats such as unauthorized access, eavesdropping, message replay, Man-in-the-Middle (MITM) attacks, and impersonation can compromise patient safety. Attackers may manipulate device settings, disrupt treatment, or even shut down devices remotely. Denial of Service (DoS) attacks can pose life-threatening risks by interrupting communication and draining battery power. Additionally, vulnerabilities in IMD firmware and remote attacks targeting network-connected medical devices can serve as entry points to hospital networks, endangering both patient data and critical infrastructure [8,9].

As medical data become increasingly susceptible to breaches, addressing security challenges and mitigating emerging threats in healthcare organizations is crucial. *Medical device security* aims to ensure that devices function correctly even under malicious attacks. This principle aligns with McGraw's definition of software security as "building software to be secure from the ground up, so that it continues to function correctly under malicious

attack” [10]. This encompasses hardware and software protections against both intentional and unintentional threats [11].

Healthcare systems require strict security and safety standards to protect patient data and maintain system integrity. However, resource constraints—especially in IMDs—render traditional security measures impractical. Limited power and storage capacity prevent the deployment of antivirus software, as it could rapidly deplete battery life and introduce new vulnerabilities. Additionally, memory constraints hinder the use of standard security software and complicate timely vulnerability patching, as updates necessitate re-certification.

In this complex landscape, adopting the *security-by-design* paradigm is imperative. Unlike reactive approaches that address vulnerabilities post-exploitation, this proactive methodology integrates security measures from the initial stages of system design, ensuring robust protection against potential threats [12].

Unfortunately, current regulations in many jurisdictions often emphasize general recommendations for medical device cybersecurity rather than specifying mandatory security requirements; for example, the U.S. Food and Drug Administration (FDA) provides cybersecurity guidance documents that describe recommended practices, but these are not legally binding requirements except where they intersect with broader quality system regulations [13]. Similarly, while the European Union’s Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) establish general safety and performance requirements, they do not lay out concrete cybersecurity obligations; instead, the MDCG 2019-16 guidance provides only non-binding recommendations [14–16]. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) issues guidance aligned with international norms, framing cybersecurity largely in terms of best practices [17]. India’s Central Drugs Standard Control Organization (CDSCO) has limited prescriptive detail on cybersecurity, relying on adherence to international standards [18]. While compliance is enforced by notified bodies and regulators, much of the cybersecurity content is advisory rather than prescriptive, creating an environment where manufacturers may lack clear and actionable obligations.

Moreover, post-market solutions often struggle to accommodate device constraints such as limited computational resources, rendering security patching impractical or even infeasible for certain devices [11]. This persistent gap is compounded by the prevalent lack of specialized cybersecurity training and the scarcity of design-support tools specifically tailored to the unique constraints of medical devices [19].

A major challenge in developing such tools and training programs is the heterogeneity and sheer volume of relevant security information. Security resources span diverse formats from regulatory texts and standards to technical threat databases, which can complicate effective retrieval, analysis, and integration. These data integration barriers significantly raise the complexity and cost of developing robust cybersecurity support tools for medical device manufacturers.

### *Our Contribution*

To enhance awareness of cybersecurity issues in medical devices, this work proposes a methodology for streamlining the communication of critical information to development and design teams in the medical industry. Our approach introduces a Cyber Threat Information Sharing (CTIS) platform built on the open-source Malware Information Sharing Platform (MISP) threat sharing system. This platform aggregates data from various sources into a centralized hub, improving accessibility and facilitating collaboration among different stakeholders.

By defining custom structures and taxonomies specifically tailored to medical devices, we establish a standardized data representation format that enhances usability. In particular, we introduce two custom data structures: one for Industrial Control Systems Medical Advisory

(ICSMA), and another for vulnerable medical devices. In our opinion, the latter is especially valuable, since it enables the creation of content that is highly relevant to platform users.

To summarize, our contributions are as follows:

- An MISP-based CTIS platform for medical devices.
- A custom taxonomy for representing vulnerable medical devices.
- Integration of this taxonomy into MISP's IoC events to enhance information usability.

The remainder of this paper is organized as follows. Section 2.1 presents software and hardware methodologies applicable to device development. Section 3 presents the most relevant vulnerability sources chosen. To address the heterogeneity of their provided information, Section 4 introduces our custom taxonomy for representing vulnerable medical devices and details MISP as the chosen platform for data collection and utilization. Section 5 explains how we tailored MISP structures to our needs, while Section 6 highlights some interesting use cases. Finally, conclusions are drawn at the end of the paper.

## 2. Background

### 2.1. Device Development Methodologies

Adopting a security-by-design approach is crucial to minimizing device vulnerabilities by embedding security considerations throughout the entire device lifecycle, from initial design to deployment and maintenance [20]. The implementation of rigorous security practices at all stages encompasses both software and hardware components to facilitate proactive threat mitigation, thereby reducing the risk of external attacks and operational failures.

#### 2.1.1. Secure Software Development

Secure Software Development (SSD) [21] involves the integration of security principles and best practices throughout the entire software development life cycle (SDLC). This methodology ensures that security is an integral consideration at every phase, from planning and design through to implementation, verification, and maintenance. The adoption of *Secure Software Development Frameworks* (SSDFs) such as NIST's SSDF [22], the OWASP Software Assurance Maturity Model (SAMM) [23], Microsoft's Security Development Lifecycle (SDL) [24], or compliance with ISO/IEC 27034 for application security [25] is particularly critical. Organizations are often required to establish a *Secure Development Policy*, especially those aiming for compliance with standards such as SOC 2 Type 2 [26] or ISO 27001 [27]. Such policies provide structured guidelines and procedures to minimize vulnerabilities across the SDLC. Furthermore, they offer a framework for evaluating and demonstrating security at each development stage, integrating risk management strategies to ensure comprehensive protection.

The use of SDLC as a solution to address cybersecurity challenges in life-saving devices was previously proposed in [28]. The author emphasized that following secure SDLC processes can mitigate threats and vulnerabilities, thereby ensuring the safety of critical systems and devices vital to human life.

#### Threat Modeling and Security Requirements Planning

SSD prioritizes proactive risk identification and mitigation, employing techniques such as threat modeling and risk assessment. A core aspect is the design of secure architectures that minimize the attack surface and implement defense-in-depth strategies.

#### Secure Coding

Secure coding refers to the adoption of programming practices that prioritize software security by minimizing vulnerabilities, protecting sensitive data, and ensuring resilience against

attacks. Secure coding employs techniques such as input validation, proper error handling, and secure data storage to mitigate common security risks. To maintain robust security measures, developers must remain informed about emerging vulnerabilities, attack vectors, and evolving best practices. Furthermore, secure coding necessitates the implementation of appropriate cryptographic algorithms and secure communication protocols to safeguard data both in transit and at rest. A key principle of secure coding is the *principle of least privilege*, which dictates that software components should only possess the minimum access rights necessary to perform their functions. To promote consistent security practices, secure coding adheres to established standards and guidelines, such as the SEI CERT Coding Standards [29] and the CERT Secure Coding Practices [30]. In addition, resources such as the OWASP Secure Coding Practices [31] provide practical checklists and recommendations, while the OWASP Top 10 [32] identifies the most critical web application security risks, helping developers to prioritize threat mitigation. By following these best practices and resources, developers can enhance software security, mitigate risks, and build trustworthy applications that resist malicious activities.

#### Code Review, Security Testing and Secure Configuration Management

Effective SSD incorporates rigorous code review practices involving regular examination of code for potential security issues and ensuring adherence to secure coding standards. Complementing this, security testing is vital, including the utilization of methodologies such as penetration testing, vulnerability scanning, and detailed code analysis to detect and remediate security flaws. Furthermore, secure configuration management is essential for implementing and maintaining secure settings for software systems and their operational environments.

#### Security Awareness Training, Regular Updates and Patches, Vulnerability Management and Incident Response

A comprehensive SSD strategy also encompasses several ongoing critical processes. Security awareness training for developers is fundamental, enhancing their ability to implement secure coding practices and stay informed about emerging threats. The consistent application of regular updates and patches is crucial for addressing known vulnerabilities and protecting against new threats. Effective vulnerability management involves a continuous process of identifying, assessing, and remediating security weaknesses. Finally, a well-defined incident response plan must be in place, outlining procedures for containment, eradication, and recovery in the event of a security breach. These critical processes are supported by secure deployment practices such as proper server and network configuration, secure update mechanisms, and robust access controls, and are maintained through continuous security monitoring post-deployment to ensure ongoing protection.

##### 2.1.2. Hardware Security

To ensure the security and integrity of medical devices, robust hardware security measures must be implemented. While network-based attacks are well documented, the hardware itself can also serve as an attack vector, especially when an attacker has physical access to the device [33,34]. This risk is significant for implantable or wearable medical devices, which may be exposed in public spaces such as hospitals, stadiums, or transportation hubs.

Medical devices should be designed to resist unauthorized physical access through tamper-evident enclosures, anti-tampering sensors, and protective coatings that hinder hardware modification. Electromagnetic shielding and power isolation reduce susceptibility to Electromagnetic Interference (EMI) and Power Side-Channel (PSC) attacks [35,36]. Secure boot mechanisms, firmware integrity checks, and cryptographic authentication

protocols help to prevent unauthorized code execution and data extraction. Strong authentication methods such as multi-factor authentication and role-based access control, ensure that only authorized entities can interact with the device.

Despite these measures, certain attacks remain a concern. EMI-based attacks can induce voltage or current fluctuations in analog sensors, potentially causing unintended or dangerous device behaviors such as accidental pacemaker discharges [35]. Out-of-band signal injection attacks exploit the physical response of a device to unintended signal frequencies, interfering with its normal function [37]. PSC attacks allow attackers to extract cryptographic keys or sensitive data by analyzing electromagnetic emissions or power consumption patterns [36]. While these attacks are particularly effective against large on-site medical equipment such as MRI or X-ray machines, they are less feasible for implanted devices due to their proximity requirements.

Hardware security is essential for protecting medical devices from both cyber and physical threats. Implementing tamper resistance, isolation, secure firmware management, and strong authentication reduces the risk of attacks. Although hardware attacks such as EMI manipulation and PSC remain a concern, well-designed security frameworks significantly mitigate potential exploits, ensuring patient safety and data integrity.

### 3. Data Sources

A proper medical device development process that incorporates security-by-design requires a thorough understanding of the existing threats and attack surfaces specific to the device in question. Knowledge of known vulnerabilities present in similar devices is also crucial. The sources of this information are diverse and varied. In particular, we believe that the three most relevant sources are *Common Vulnerabilities and Exposures* (CVE), *Industrial Control Systems Medical Advisory* (ICSMA), and the scientific literature.

#### 3.1. CVE

Common Vulnerabilities and Exposures (CVE) is a publicly accessible dictionary of known cybersecurity vulnerabilities and exposures, each identified by a unique CVE ID. These IDs are used to track and coordinate vulnerability information across different security tools and services.

CVE IDs are assigned by *CVE Numbering Authorities* (CNAs) [38], which include security researchers, software vendors, and government agencies authorized by the CVE Program [39]. While CVEs are primarily associated with software vulnerabilities, they can also be assigned to hardware, firmware, and other system components.

When a CVE is assigned, a corresponding record is created in the CVE database. Each record contains details about the vulnerability, including its description, impact, and remediation steps. Additionally, CVEs are used to generate *Common Vulnerability Scoring System* (CVSS) scores, which quantify the severity of vulnerabilities. These scores help security professionals to prioritize remediation efforts and inform their risk management decisions.

CVEs play an important role in vulnerability management by providing a standardized framework for describing and classifying vulnerabilities. This standardization enhances communication and collaboration among security professionals, making vulnerability information more accessible and ultimately improving the security of software and systems.

#### 3.2. ICSMA

An Industrial Control Systems (ICS) Medical Advisory (ICSMA) is a security advisory issued by the *Cybersecurity and Infrastructure Security Agency* (CISA) [40], to alert healthcare organizations about vulnerabilities and exploits that could affect ICS medical devices such as ventilators, anesthesia machines, and dialysis machines.



ICSMAAs provide healthcare organizations with essential information, including details on identified vulnerabilities and exploits, the specific medical devices and manufacturers affected, and the potential impact on device functionality. Additionally, they offer recommended mitigation strategies to safeguard medical devices along with references to further resources such as vendor security patches and technical guidance.

As a vital resource for healthcare organizations, ICSMAAs help strengthen the security of medical devices. By regularly reviewing these advisories and implementing appropriate mitigation measures, healthcare organizations can reduce the risk of cyberattacks and enhance patient safety.

### 3.3. Scientific Literature

CVEs and ICSMAAs are inherently valuable sources of certified information. An additional valuable contribution may come from the scientific literature, which offers complementary insights into documented CVEs and may provide critical information relevant to the secure development of medical devices.

## 4. Data Classification and Sharing

As discussed in Section 3, the sources of information relevant to a secure medical device development process are diverse and heterogeneous. When this information is structured, each source typically employs a different data representation. Consequently, accessing all available information requires users to be familiar with multiple “languages”. These users include not only individuals involved in the device development process but also automated systems responsible for verifying security.

For these reasons, it is crucial to adopt a standardized format for data representation. Such a format harmonizes input from various sources and facilitates interoperability between information repositories and medical device development and testing systems. Specifically, a common format should enable different entities to extend its content, incorporating new information from diverse sources to enhance its utility.

### 4.1. Medical Device Taxonomy

A taxonomy has been defined to classify medical devices and explicitly represent information regarding their security and vulnerabilities. This taxonomy is promoted by the *Cyber4Health* Observatory on Cyber and Physical Vulnerabilities in Medical Devices [41], and profiles devices based on the eight key criteria reported in Table 1.

- *Body District*—The specific body part the device is intended to affect (e.g., heart, stomach).
- *Product Type*—The category of medical device based on function (e.g., insulin pumps, pacemakers).
- *Device Type*—Classification into *wearables* (e.g., insulin pumps), *implantables* (e.g., pacemakers), *smartwatches*, or *on-site* devices.
- *Year*—The year in which the vulnerability was discovered.
- *Attack Type*—The nature of potential attacks the device is susceptible to (e.g., cyber, physical).
- *Vulnerability Type*—The type of detected vulnerability (e.g., lack of encryption, lack of authentication).
- *Vulnerability Severity*—The CVSS score assessing the severity of the vulnerability.
- *Risk Class*—The device hazard classification, either *I*, *Ila*, *Ilb*, or *III*.

**Table 1.** Taxonomy used to classify vulnerable medical devices.

| Criterion                     | Description                                                                  |
|-------------------------------|------------------------------------------------------------------------------|
| <i>Body District</i>          | Anatomical region where the device is applied (e.g., heart, stomach, brain). |
| <i>Product Type</i>           | Functional category of the device (e.g., insulin pump, pace-maker).          |
| <i>Device Type</i>            | Usage-based classification: wearable, implantable, on-site, etc.             |
| <i>Year</i>                   | Year in which the vulnerability was discovered or reported.                  |
| <i>Attack Type</i>            | Nature of attacks: cyber (e.g., network-based), physical, or hybrid.         |
| <i>Vulnerability Type</i>     | Type of security flaw (e.g., lack of encryption, default credentials).       |
| <i>Vulnerability Severity</i> | CVSS score indicating the criticality of the vulnerability.                  |
| <i>Risk Class</i>             | Regulatory risk classification (e.g., Class I, IIa, IIb, III).               |

This taxonomy is fundamental in defining the data format used in our solution, which is detailed in Section 5.

#### 4.2. European Medical Device Nomenclature

Article 26 of Regulation (EU) 2017/745 on medical devices [14] and Article 23 of Regulation (EU) 2017/746 on in vitro diagnostic medical devices [15] mandate that the European Commission provide, free of charge, a nomenclature of medical devices recognized at the international level [42]. This list is open to update proposals from various stakeholders, including competent authorities, notified bodies, the World Health Organization (WHO), trade associations, manufacturers, authorized representatives, importers, and distributors. Proposals can be submitted throughout the year following a dedicated procedure; at the end of each year, a revised version of the list is published. Manufacturers use this nomenclature for registering medical devices in the EUDAMED database [43].

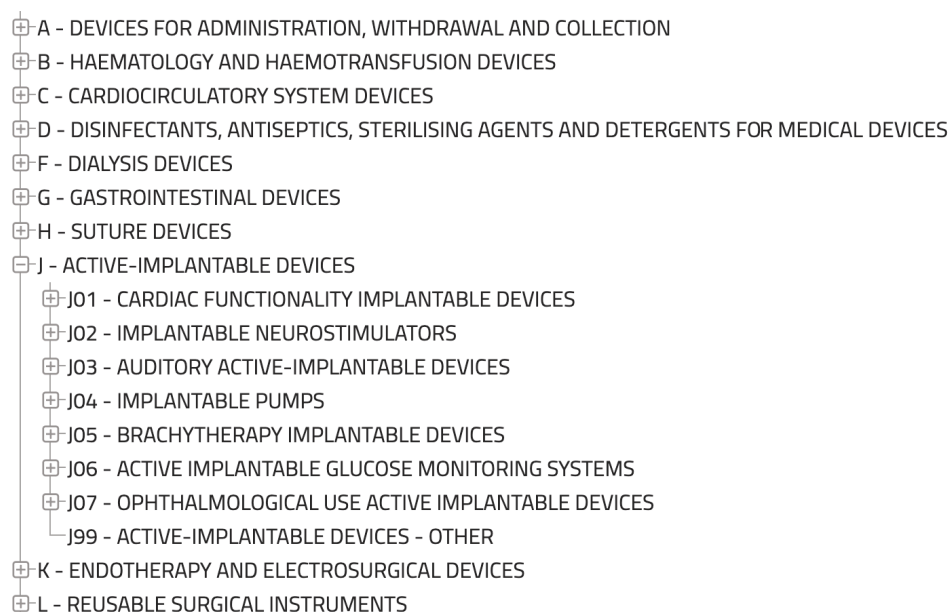
As illustrated in Figure 1, the EMDN follows a hierarchical structure, allowing for a detailed classification of medical devices based on their specific characteristics.

Thus, the EMDN serves as a valuable, internationally recognized, and standardized classification tool that can be leveraged to refine the data format used in our solution.

#### 4.3. Data Sharing Tools: MISP

The *Malware Information Sharing Platform* (MISP) [44] threat sharing tool is an open-source threat intelligence platform designed to enhance cybersecurity efforts by facilitating the exchange of threat intelligence among organizations and communities worldwide. Its primary goal is to strengthen collective defense against cyber threats by enabling structured and collaborative threat information sharing.

MISP serves as a central repository where organizations can share and analyze a wide range of threat intelligence data, including *indicators of compromise* (IoCs), malware samples, attack techniques, and *tactics, techniques, and procedures* (TTPs). By leveraging shared intelligence, organizations can proactively enhance their security posture.



**Figure 1.** Subset of the EMDN.

A key feature of MISP is its standardized data format, which ensures consistency and interoperability across different organizations and platforms. The platform is highly extensible and integrates seamlessly with various cybersecurity tools, including Security Information and Event Management (SIEM) systems, Intrusion Detection/Prevention Systems (IDS/IPS), and firewalls. It supports diverse data import and export formats, making it adaptable to different security infrastructures.

One of MISP's core functionalities is IoC management, allowing organizations to collect, update, and share IoCs in real time. It aggregates threat intelligence from multiple sources, including commercial, open-source, and community-contributed feeds, providing up-to-date insights into emerging threats.

MISP fosters collaboration by enabling the creation of private or community-specific threat-sharing groups, allowing organizations to share intelligence within trusted networks. Additionally, the platform offers powerful tools for threat analysis and visualization, helping analysts identify correlations, uncover hidden relationships, and detect patterns that might not be evident when analyzing individual indicators.

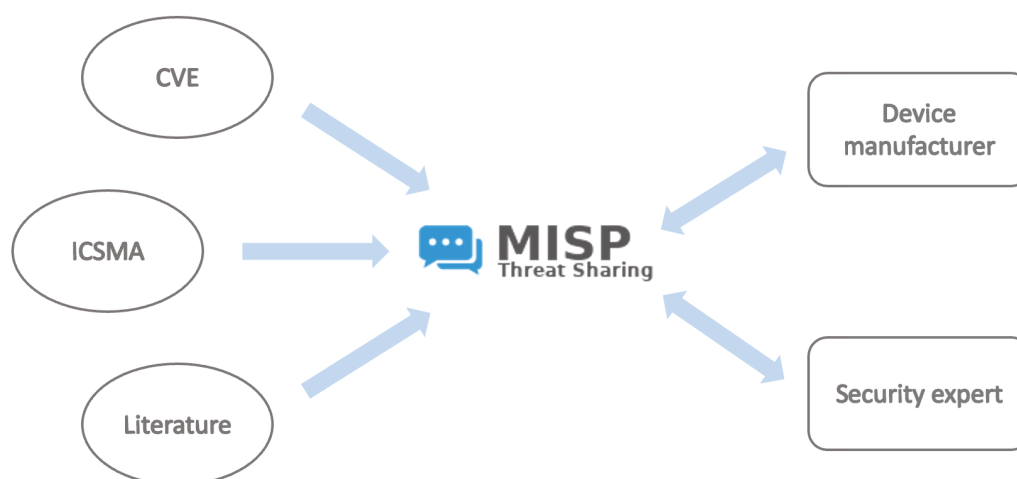
In incident response, MISP provides a structured framework for documenting and handling incidents. Analysts can attach threat intelligence data to incidents, aiding in risk assessment and mitigation. The platform also emphasizes privacy and data-sharing controls, allowing organizations to define granular access permissions to ensure compliance with legal and regulatory requirements.

MISP's development is continuously supported by an active community of cybersecurity professionals, fostering innovation and ensuring its relevance in the ever-evolving cyber threat landscape.

## 5. Medical MISP

Our solution leverages MISP to develop a Cyber Threat Information Sharing (CTIS) platform specifically tailored for medical devices, which we call *MMISP*. This platform is designed to collect and consolidate information from the various sources mentioned in Section 3 to provide a unified data repository and facilitating seamless interaction among the different entities involved, as illustrated in Figure 2.





**Figure 2.** CTIS Architecture: Information sourced from CVE, ICSMA, and the scientific literature (**left**) feeds into the MISP platform (**center**), which organizes and processes the data for use by relevant entities such as device manufacturers and security experts (**right**).

In particular, we utilize two types of IoC events: *CVE* and *ICSMA*. To manage these event categories effectively, it is essential to define their respective structures. The MISP platform includes a default structure for IoC events related to CVEs; therefore, we only define a custom structure for ICSMA events. This structure incorporates all of the relevant information outlined in Section 3.2, including details on vulnerabilities and associated CVEs, affected medical devices, potential impacts, and recommended mitigations. Figure 3 presents an example of an ICSMA event, showcasing a subset of attributes within the defined structure.

|                                  |                                                                                                                                                                                                                                                                                                                            |  |                                     |      |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-------------------------------------|------|
| <b>ICSMA:</b><br>link            | <a href="https://www.cisa.gov/news-events/ics-medical-advisories/icsma-23-103-01">https://www.cisa.gov/news-events/ics-medical-advisories/icsma-23-103-01</a>                                                                                                                                                              |  | <input checked="" type="checkbox"/> | 1879 |
| <b>Alert code:</b><br>text       | ICSMA-23-103-01                                                                                                                                                                                                                                                                                                            |  | <input type="checkbox"/>            |      |
| <b>Affected product:</b><br>text | Battery pack SP with Wi-Fi (SN 138853 and higher) with software 053L000091 (global) / 054U000091 (U.S.) and 053L000092 (global) / 054U000092 (U.S.)                                                                                                                                                                        |  | <input type="checkbox"/>            |      |
| <b>Risk evaluation:</b><br>text  | Successful exploitation of this vulnerability could allow a sophisticated and authenticated attacker to compromise the security of the Space communication device Battery Pack SP with Wi-Fi. An attacker could escalate privileges, view sensitive information, upload arbitrary files, and perform remote code execution |  | <input type="checkbox"/>            |      |
| <b>Vulnerability:</b><br>text    | Improper neutralization of directives in dynamically evaluated code ('Eval Injection')                                                                                                                                                                                                                                     |  | <input type="checkbox"/>            |      |
| <b>Equipment:</b><br>text        | Battery Pack SP with Wi-Fi                                                                                                                                                                                                                                                                                                 |  | <input type="checkbox"/>            |      |
| <b>Vendor:</b><br>text           | B. Braun Melsungen AG                                                                                                                                                                                                                                                                                                      |  | <input type="checkbox"/>            |      |
| <b>ATTENTION:</b><br>text        | Exploitable remotely/low attack complexity                                                                                                                                                                                                                                                                                 |  | <input type="checkbox"/>            |      |
| <b>CVSS v3:</b><br>float         | 5.5                                                                                                                                                                                                                                                                                                                        |  | <input type="checkbox"/>            |      |

**Figure 3.** Illustration of an ICSMA event within the MISP platform. The visualization includes the external ICSMA reference, details on affected products, risk evaluation, vendor information, and related attributes.

Additionally, an effective vulnerability management strategy for medical devices must consider not only vulnerabilities that directly affect the device firmware or hardware but also those present in third-party libraries and components embedded within the device software. To this end, maintaining an up-to-date Software Bill of Materials (SBOM)—a detailed inventory of all software components, including libraries and dependencies—is essential.

An SBOM enables rapid identification of vulnerable components when new CVEs or ICSMAs are published, facilitating timely remediation. Moreover, initiatives and tools have

emerged to automatically generate SBOMs from binary files, addressing situations where vendors do not provide this information.

Integrating SBOM management within MMISP would enhance its capability to track and correlate vulnerabilities across the entire software stack of medical devices, strengthening overall device security.

While Sections 3.1 and 3.2 highlight the importance of IoC events for CVEs and ICSMAs, these two event types alone do not allow for an immediate identification of security issues related to specific categories of medical devices. To address this gap, we introduce a third dedicated structure that bridges the gap between these IoC events and medical device developers. This structure, referred to as *Medical Device*, is defined according to the taxonomy described in Section 4.1. It contains key information such as device and manufacturer details, known attacks and vulnerabilities, possible countermeasures, and associated ICSMAs. Figure 4 illustrates an example of a Medical Device event, displaying a selection of attributes that make up the corresponding structure.

|                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |
|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------|
| Vendor:                                  | B. Braun Melsungen AG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    |    |    |    | <input type="checkbox"/> |    |
| text                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |
| Product name:                            | Battery Pack SP with Wi-Fi                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |    |    |    |    | <input type="checkbox"/> |    |
| text                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |
| Publication year:                        | 2023-07-10T00:00:00.000000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |    |    |    |    | <input type="checkbox"/> |    |
| datetime                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |
| Description of the attack/vulnerability: | An improper neutralization of directives in dynamically evaluated code vulnerability in the Wi-Fi Battery embedded web server versions L90/U70 and L92/U92 can be used to gain administrative access to the Wi-Fi communication module. An authenticated user, having access to both the medical device Wi-Fi network (such as a biomedical engineering staff member) and the specific B. Braun Battery Pack SP with Wi-Fi web server credentials, could gain administrative (root) access on the infusion pump communication module. |    |    |    |    | <input type="checkbox"/> |    |
| text                                     | <a href="#">Show all</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |
| Possible countermeasures:                | B. Braun has released software updates to mitigate the reported vulnerabilities: Battery pack SP with Wi-Fi: software 053L000093 (global) / 054U000093 (U.S.). Facilities in Canada utilizing "U" versions of the software should follow the U.S. version. Facilities in Canada utilizing non-"U" versions (e.g. L) should follow the global version. The infusion pumps are not directly affected. However, the interrupted network communication might prevent certain features of the device from functioning properly.            |  |  |  |  | <input type="checkbox"/> |  |
| text                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                     |                                                                                      |                                                                                       |                                                                                       |                          |                                                                                       |

**Figure 4.** Example of a Medical Device event in MISP. The visualization highlights IoCs along with vendor, product name, vulnerabilities, and related attributes.

### 5.1. Event Tag Taxonomy

To further enhance and extend the search capabilities for relevant information, a taxonomy has been defined to generate labels that can be associated as tags with Medical Device IoC events. This taxonomy is derived from a subset of the search criteria outlined in Sections 4.1 and 4.2.

By leveraging these tags, events can be filtered based on attributes such as risk class, potential attack vectors, or device type. This tagging system enables both visual and automated classification of events according to specific characteristics. An example of an event list on the MISP platform is shown in Figure 5, with some events associated with tags of different colors.

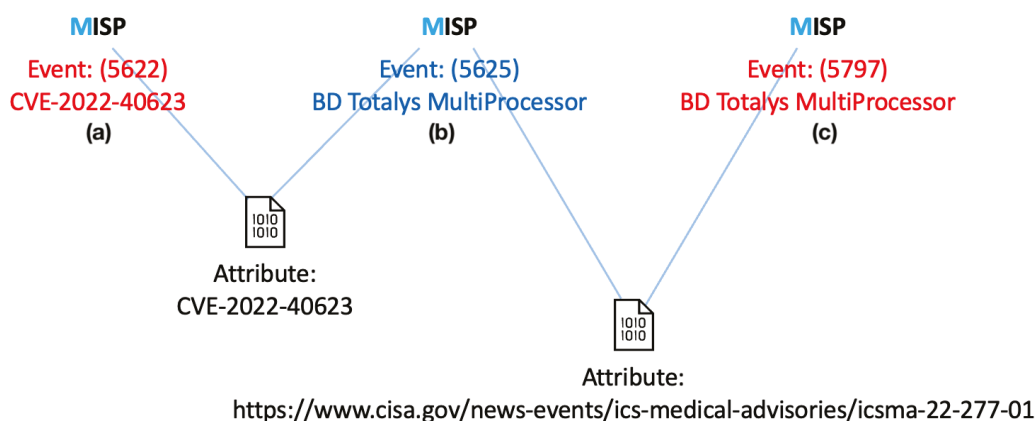
| Tags                                                                                                                 |                                                                                                                      |                                                          | Enter value to search | Event info | Filter | #Attr | #Corr | Info                           |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------|------------|--------|-------|-------|--------------------------------|
| medical-device-vulnerability-product-type=insulin-pump                                                               | medical-device-vulnerability-body-district-application=blanush                                                       | medical-device-vulnerability-risk-class=fa               |                       |            |        | 4     |       | Insulin Pump                   |
| medical-device-vulnerability-demonstrated=demonstrated                                                               | medical-device-vulnerability-vulnerabilities=Lack of encrypted mechanism                                             | medical-device-vulnerability-type-of-the-attack=Cyber    |                       |            |        |       |       |                                |
| medical-device-vulnerability-type-of-device=implantable                                                              | medical-device-vulnerability-attack=Evareschopping                                                                   | medical-device-vulnerability-attack=Impersonation        |                       |            |        | 3     | 1     | Oximeter                       |
| medical-device-vulnerability-product-type=wearable                                                                   | medical-device-vulnerability-body-district-application=Forep                                                         | medical-device-vulnerability-risk-class=fa               |                       |            |        |       |       |                                |
| medical-device-vulnerability-vulnerabilities=Lack of security PIN required for pairing                               | medical-device-vulnerability-type-of-the-attack=Cyber                                                                | medical-device-vulnerability-demonstrated=demonstrated   |                       |            |        |       |       |                                |
| medical-device-vulnerability-attack=MITM                                                                             | medical-device-vulnerability-attack=Replay Attack                                                                    | medical-device-vulnerability-type-of-device=Wearable     |                       |            |        |       |       |                                |
| medical-device-vulnerability-product-type=pacemaker                                                                  | medical-device-vulnerability-body-district-application=Heart                                                         | medical-device-vulnerability-risk-class=fa               |                       |            |        | 8     | 12    | Medtronic InSync & Adapta      |
| medical-device-vulnerability-vulnerabilities=Lack in the analog components, inadequate protection against "backdoor" | EM coupling                                                                                                          | medical-device-vulnerability-type-of-the-attack=Physical |                       |            |        |       |       |                                |
| medical-device-vulnerability-type-of-device=implantable                                                              | medical-device-vulnerability-attack=EM Signal Injection                                                              |                                                          |                       |            |        |       |       |                                |
| medical-device-vulnerability-product-type=cardiac-resynchronization-therapy-defibrillator (CRT-D)                    | medical-device-vulnerability-body-district-application=Heart                                                         | medical-device-vulnerability-risk-class=fa               |                       |            |        | 8     | 3     | Boston Scientific Cognia 100-D |
| medical-device-vulnerability-demonstrated=demonstrated                                                               | medical-device-vulnerability-vulnerabilities=Lack in the analog components, inadequate protection against "backdoor" | EM coupling                                              |                       |            |        |       |       |                                |
| medical-device-vulnerability-type-of-the-attack=Physical                                                             | medical-device-vulnerability-type-of-device=implantable                                                              | medical-device-vulnerability-attack=EM Signal Injection  |                       |            |        |       |       |                                |

**Figure 5.** Example of MISP's events list, showing four Medical Device events with associated tags. The '#Corr.' column indicates the number of IoC events related to the selection.

### 5.2. Event Correlation

An essential feature of the MISP platform is its ability to correlate IoC events based on specific attributes. The selection of correlatable attributes can be tailored to individual needs, allowing for a more focused or broader retrieval of related IoC events.

For instance, this correlation mechanism enables the retrieval of information on associated ICSMAs or CVEs starting from a specific Medical Device. Similarly, it allows identifying other Medical Devices linked to the same ICSMA or CVE. Figure 6 illustrates an example of correlation between a CVE, an ICSMA, and a Medical Device.



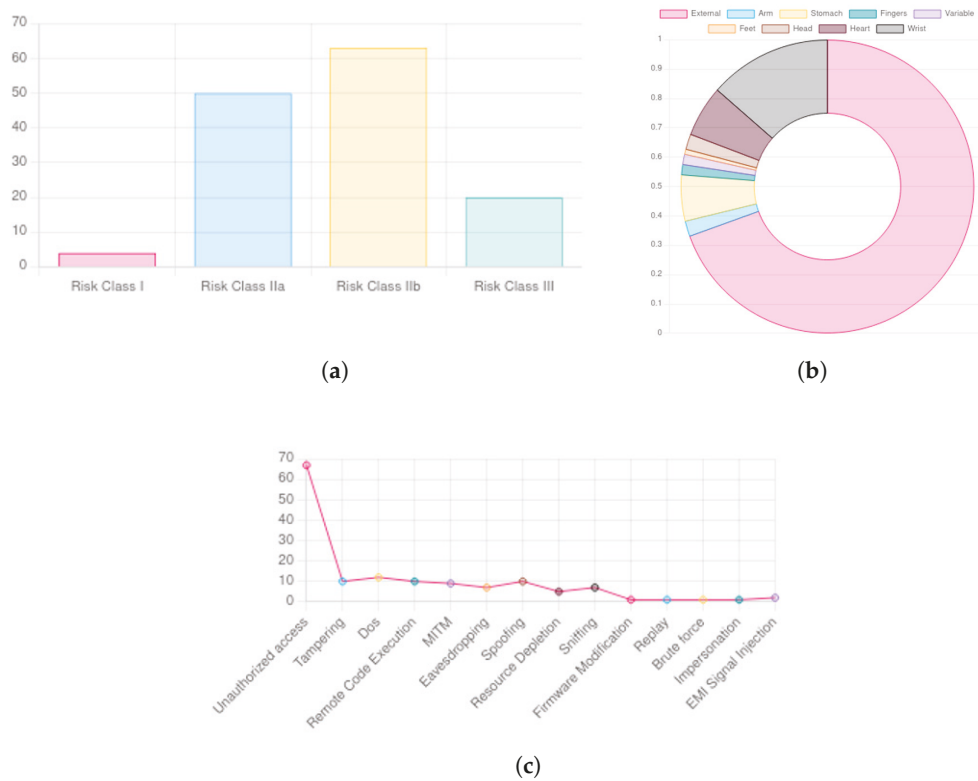
**Figure 6.** Example of IoC event correlation: First, a CVE event (a) is linked to an ICSMA event (b) via the 'CVE ID' attribute; then the ICSMA event is correlated with a Medical Device event (c) through the 'ICSMA external link' attribute (<https://www.cisa.gov/news-events/ics-medical-advisories/icsma-22-277-01>, accessed on 10 July 2025).

### 5.3. MISP Dashboard

The MISP platform provides a customizable "Dashboard" feature, allowing users to integrate widgets that highlight relevant information. Figure 7 presents an example where we have developed custom widgets to visually represent analyses conducted on IoC events within the system.

Specifically, Figure 7a illustrates the classification of IoC events based on the risk class of the associated medical devices. Figure 7b categorizes events according to the body regions where the affected devices are applied. Lastly, Figure 7c displays classifications based on the type of potential attacks.

The use of charts and other visualization techniques greatly enhances data interpretability within the platform. This added level of abstraction makes the information accessible to non-technical users while preserving the necessary technical depth.



**Figure 7.** IoC events visualization: (a) risk class, (b) body district, (c) attack type.

## 6. MMISP Use Case

To illustrate how MMISP supports the security-by-design paradigm, we present the following use case. A development team is designing a new medical device for monitoring and collecting vital patient data. Given the critical importance of patient data security, the team aims to ensure that the device is resilient to cyber threats and compliant with security standards. The team leverages MMISP to access historical vulnerability data from similar medical devices and components already deployed in the field, enabling informed design decisions before the deployment of their own device. Specifically, they leverage MMISP to support the following steps:

- *Information Gathering*—The team utilizes MMISP to collect intelligence on cyber threats targeting medical devices. They focus on vulnerabilities (CVEs), products and components (CPEs), and industry-specific threats (ICSMA). For example, they identify vulnerabilities affecting widely used Bluetooth modules that are considered for integration.
- *Vulnerability Analysis*—MMISP allows the team to assess the technical details of discovered vulnerabilities, such as affected software versions and exploit availability. In one instance, a vulnerability affecting a third-party communication library prompts them to reconsider component selection.
- *Risk Assessment*—Using MMISP, the team evaluates the risks associated with each identified vulnerability, considering factors such as exploitability and potential impact.
- *Integration into the Development Process*—The team applies security insights from MMISP to strengthen their device's design. This may involve patching vulnerabilities, isolating critical components, or implementing robust authentication mechanisms.
- *Continuous Monitoring*—Throughout the device's lifecycle, the team relies on MMISP to stay informed about emerging threats and vulnerabilities, ensuring long-term security.
- *Regulatory Compliance*—The team leverages MMISP data to verify compliance with medical device security regulations and industry standards.

By proactively addressing cybersecurity risks, the development team enhances the safety and reliability of their medical device. This security-by-design approach safeguards both patient data and the integrity of the device's operations.

## 7. Limitations and Future Directions

Although MMISP provides a promising framework for integrating threat intelligence into the secure development of medical devices, the current work should be considered a proof-of-concept rather than a validated system. At this stage, the platform has not yet been deployed or tested in real-world development pipelines, and no quantitative evaluation has been conducted to measure its actual impact.

As such, one key limitation of this study is the lack of empirical validation. The examples and use cases provided are hypothetical and illustrative, and are intended to demonstrate the potential applications of MMISP rather than serve as evidence of its effectiveness. Future work should focus on designing pilot studies with medical device manufacturers where MMISP is integrated into development workflows and assessed through measurable indicators such as time-to-detection of vulnerabilities, threat coverage, and design improvement metrics. To address these aspects, future studies should: (i) validate MMISP in controlled environments through case studies and testing with development teams, and (ii) investigate the adoption of machine learning models for automated threat classification and prioritization.

Furthermore, the effectiveness of MMISP heavily relies on the establishment of a robust network of participating nodes that actively engage with the platform. It is critical that these nodes do not merely act as passive sources of information but also contribute by sharing their own vulnerability data and threat intelligence. By becoming active sources themselves, these participants can enrich the collective knowledge base, fostering a collaborative ecosystem that enhances the overall security posture of medical device development. However, incentivizing such active participation requires addressing potential barriers, including trust issues, data privacy concerns, and the development of standardized protocols for secure information sharing.

Additionally, scalability challenges must be considered as the number of participants in the network grows significantly. A substantial increase in active nodes could strain the platform's infrastructure, leading to potential bottlenecks in data processing, storage, and real-time analysis. Issues such as latency in threat information dissemination, data duplication, and the management of conflicting reports may arise, potentially undermining the platform's reliability. Future research should explore distributed architectures, load balancing mechanisms, and efficient data validation techniques to ensure that MMISP remains effective and responsive even at scale.

## 8. Conclusions

In this paper, we have emphasized the importance of adopting a security-by-design approach in the development of medical devices. We have analyzed the most important sources of both certified and non-certified information, highlighting the challenges posed by the heterogeneity of content and data representation. This variability presents a significant barrier to gaining comprehensive knowledge of the security risks associated with these devices.

The MISP platform offers a valuable solution by acting as both an aggregator and an enhancer of cybersecurity information. We have demonstrated how it can be leveraged for CTIS in the medical device domain by defining specialized IoC event structures and taxonomies. One of MISP's most powerful features—its ability to correlate events—is particularly beneficial in this context, facilitating deeper analysis and stronger security insights.



Furthermore, we have illustrated how the MISP platform can support various stages of a medical device's lifecycle, from risk assessment to continuous monitoring and regulatory compliance. In conclusion, we firmly believe that a dedicated MISP instance for medical devices can serve as a crucial tool for research, threat analysis, and the dissemination of security-related information, ultimately enhancing the protection of these critical healthcare technologies.

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# Cellulose-Based Electrochemical Sensors

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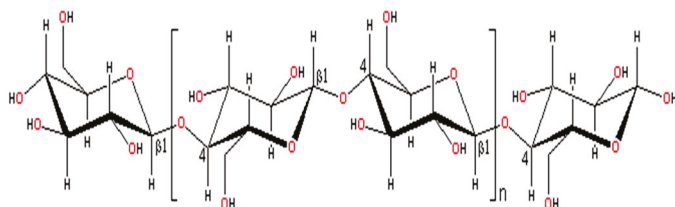
**Abstract:** Among the most promising areas of research, cellulose-based electrochemical sensors stand out for their intrinsic properties such as abundance, biocompatibility, and versatility. This review is concerned with the integration and application of cellulose-derived materials in electrochemical sensors, pointing out improvements in sensitivity, selectivity, stability, and functionality for a wide variety of applications. The most relevant developments on cellulose-based sensors have been concentrated on nanocellulose composite synthesis, advanced cellulose modification, and the successful embedding in wearable technologies, medical diagnostics, and environmental monitoring. Considering these, it is worth mentioning that significant challenges still need to be overcome regarding the scalability of production, selectivity improvement, and long-term stability under real operational conditions. Future research efforts will concern the union of cellulose-based sensors with the Internet of Things (IoT) and artificial intelligence (AI) toward wiser and more sustainable health and environmental solutions. Correspondingly, this work puts cellulose in the front line among the most perspective materials for enabling the development of eco-friendly and high-performance sensing technologies.

**Keywords:** electrochemical sensors; biocompatibility; cellulose-derived materials; environmental monitoring; medical diagnostics

## 1. Introduction

Polysaccharides such as cellulose, chitosan, alginate, and hyaluronic acid encompass enormous biomaterials. This is because of their inherent abundance on Earth and impressive physicochemical and biological attributes [1,2]. As the most abundant biopolymer on Earth, cellulose and its derivatives have been among the most studied materials in several biomedical applications, including hydrogels, aerogels, films, and fillers, due to their outstanding properties and biocompatibility [3–8]. Cellulose is a linear homopolysaccharide consisting of  $\beta$ -1,4-linked glucans and has abundant hydroxyl groups on its surface which have a formula of  $(C_6H_{10}O_5)_n$ . The chemical structure of cellulose is shown in Figure 1. It possesses a high degree of symmetry within its amphiphilic molecular structure [9–11]. Its high surface area and excellent biocompatibility, with tunable functional groups, make it a prime candidate for improving sensor performance. Its renewability, together with features tailored for a range of sensor designs, positions cellulose as an ecologically friendly yet highly efficient solution for the development of state-of-the-art, eco-friendly sensing technologies. Chemical modifications include carboxylation, esterification, and grafting of cellulose, which enhances its ability to increase electron transfer, sensitivity, and specificity in the selective identification of target analytes. By modifying cellulose, it becomes highly adaptable material for sensors, capable of detecting environmental pollutants and

biomolecules with improved efficiency [12–14]. The source of cellulose will affect its structure and properties, and these sources are as varied as plants [15] including cotton, sisal, and wood, algae [16] such as valonia, and bacterial sources including *Komagataeibacter* sp. [17]. There have been various studies that report on the extraction of cellulose from numerous biomass sources, pointing to various methods and approach developments in past years [11,18–26].



**Figure 1.** Chemical structure of cellulose.

Generally, the method for electrochemical sensing involves monitoring analyte–receptor interactions within an electrolyte solution using either potentiometry or amperometry. However, fouling—that is, the accumulation of large organic surfactants, proteins, or reactions on the electrode surface—and poor selectivity are major drawbacks for these sensors. As a result, many of them are not highly effective in some clinical and environmental applications. On the other hand, cellulose is considered one of the most promising membrane materials in overcoming such problems since it has very minimal fouling and better selectivity [27–30]. Recently, the combination of cellulose with carbon-based nanomaterials such as graphene [31], graphene oxide (GO) [32], single-walled carbon nanotubes (SWCNTs) [33], multi-walled carbon nanotubes (MWCNTs) [34], and nanodiamonds [35] has also been a very promising approach for the development of nanocomposites for various electrochemical applications, including amperometric sensing. Transparent, ultra-strong, and printable conductive nanocomposites have been developed by incorporating 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized cellulose nanofibrils (TOCNFs) with SWCNTs [33]. Recently, the stability of four different nanocomposites prepared using fibrillar nanocelluloses with different functional groups (sulfate, carboxylate, and amino-silane) and MWCNTs was tested. These nanocomposites exhibited very good stability in a wide potential window (−0.6 to +1 V) in various electrolytes [34].

In recent decades, all kinds of smart electronic devices have been developed and extended to various applications, including smart human motion tracking, flexible human–computer interfaces, touchscreen displays, energy generation, storage system, smart glazing, or actuators [36–43]. All involved sensors have been located as one of the most significant directions in this area and continue to attract broad scientific concern because of their extraordinary ability to respond to the effects of physical forces, chemical substances, and biological analytes. These sensor elements transform this input energy into an accessible, recognizable, and manageable form of a signal [44]. Based on the remarkable electrochemical properties of cellulose, we will discuss cellulose-based electrochemical sensors, focusing on their development, design, and applications.

## 2. Cellulose-Based Materials for Electrochemical Sensors

### 2.1. Types of Cellulose Used in Electrochemical Sensors

Naturally, cellulose fibers contain regions of crystalline and amorphous nature. Microcrystalline cellulose (MCC) is a refined, partially depolymerized cellulose obtained from  $\alpha$ -cellulose source [45]. However, MCC can be produced using several techniques which include reactive extrusion [46], enzyme-mediated [47], and acid hydrolysis [48–51] techniques; all these techniques remove amorphous regions, retaining the crystalline domains

with a more ordered structure. The hydroxyl groups located on the surface of the cellulose and the very well-organized structure of molecules in MCC can interact well with a range of materials, including conducting polymers [52]. MCC is mainly produced from wood and cotton [53], and its application also extends to the pharmaceutical [54], medical [55], food [56–58], and cosmetic industries [58,59] due to its wide range of applications. The usage of MCC as a reinforcement in composites, however, has been less common compared to the usage rate of lignocellulosic fibers; however, in recent years, there has been growing interest in incorporating MCC into composite materials [60–62]. Therefore, MCC has become one of the favorite candidates for composite applications because of its renewability, biodegradability, high surface area, low density, and other favorable properties [63]. A surfactant-directed microcrystalline cellulose/polyaniline composite was developed, exhibiting enhanced electrochemical properties [52].

Nanocellulose is highly attractive due to its unique properties, diversified precursors, wide application fields, and biodegradable nature [64]. Based on size, morphology, and synthesis method, nanocellulose can be categorized as cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) [65–67]. Traditionally, CNCs are produced through chemical routes where hydrolysis produces short rod-shaped particles with diameters between 3 and 10 nm [68–70]. Most CNFs have been produced mechanically by ball milling, grinding, and homogenization techniques that generate flexible, fibril-shaped particles [71, 72]. Dimensions of both CNCs and CNFs can be reduced using ultrasonication during processing [73–75]. In general, CNCs have dimensions smaller than CNFs, which gives them a higher crystallinity index, and hence they can act more effectively as reinforcing agents in various polymer matrices. On the other hand, CNFs represent long flexible fibers with a larger diameter, and due to longer and smaller diameter fibrils, they offer a better reinforcing effect [76,77]. Nanocellulose is invariably combined with active materials to develop its application areas. The synergistic relation between nanocellulose and the involved materials has been key in accomplishing state-of-the-art physical sensors, chemical sensors, or biosensors with high performance in different dimensions. Various associated fabrication techniques enabled the development and construction of nanocellulose-based sensors for a series of applications [78–83]. Several reviews have documented the use of nanocellulose in sensor applications [84–88].

Because of the high purity and peculiar physicochemical properties, microbial cellulose synthesized by bacteria known as bacterial cellulose (BC) can be regarded as a source of pure cellulose [89]. Its uses include applications in food [90], biomedical [91–94], production of bio-based polymers, and nanocomposites [95–97]. Only a few species of bacteria are known to synthesize cellulose, and among the prominent ones is *Gluconacetobacter xylinus*, previously called *Acetobacter xylinum* [98]. This Gram-negative, rod-shaped, aerobic bacterium produces cellulose at very high yields like microfibrils, making it a model organism to produce bacterial cellulose (BC) [99]. Other bacterial genera that can produce BC include *Agrobacterium* spp., *Acetobacter* spp., *Azotobacter*, *Rhizobium* spp., *Sarcina*, *Alcaligenes*, and *Pseudomonas* [89]. *Acetobacter*, a genus of vinegar bacteria, is a non-photosynthetic advanced purple bacterium capable of converting glucose, glycerol, sugars, and other organic compounds into pure cellulose [100]. Several different composites of bacterial cellulose have been developed by modifying the bacterial growth conditions, introducing a secondary phase, and including materials like starch, collagen, hydroxyapatite, carbon nanotubes, and graphene [101–106]. These additions have enabled an improvement in some properties of high interest, including biocompatibility [102] and electrical conductivity [101,105,107]. Various enzymes, including laccase and heme proteins such as glucose oxidase (GOx) and horseradish peroxidase, have been immobilized into BC-based networks to develop electrochemical biosensors aimed at detecting compounds like H<sub>2</sub>O<sub>2</sub>,

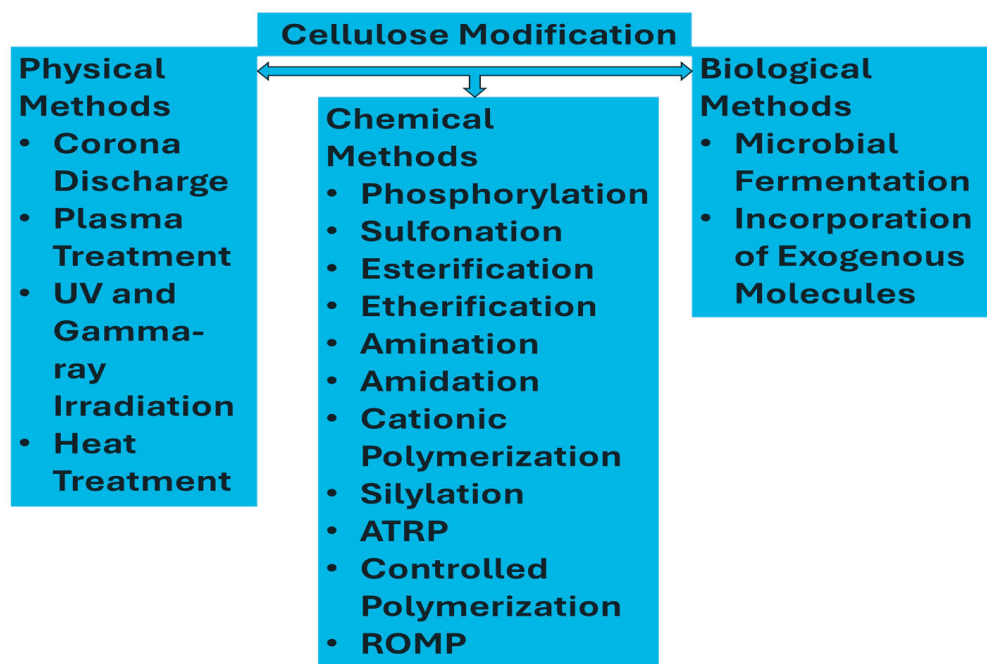
hydroquinone, dopamine, and glucose [108–112]. Biosensors made from BC are produced by combining it with various materials, and they are classified according to their origin and potential uses [107,113–115]. For example, an electrochemical biosensor was successfully developed using a BC substrate for lactate detection in artificial sweat [28].

## 2.2. Modifications of Cellulose

The modification of cellulose primarily focuses on improving its adsorption properties by altering its surface. The structure of cellulose consists of tetrahydropyran units connected by 1–4 glycosidic bonds, each containing a hydroxyl (-OH) and primary alcohol (-CH<sub>2</sub>OH) group. During modification, the active hydroxyl group, particularly the one attached to the primary alcohol, is replaced with other functional groups, thereby enhancing the desired properties of the material [116,117]. Classification of the cellulose modification methods is presented in Figure 2. Among the physical methods, corona discharge [118], plasma treatment [119–121], UV and gamma-ray irradiations [122–124], and heat treatment [125,126] modify the surface properties of cellulose fibers without the involvement of harsh chemicals. Corona discharge treatment includes the introduction of high-energy electrons via high-frequency discharges to facilitate the creation of cavities and micropores on the fiber surface. Oxygen plasma treatment effectively modifies bacterial cellulose membranes by enhancing hydrophilicity and introducing structural changes, while water permeability is reduced, resulting in the improved selectivity of membranes. Gamma radiation or other forms of radiation-based techniques exploit crosslinking within the polymer chain and are useful in altering the properties of cellulose-reinforced biopolymer composites. This results basically in the modification of the composite structure and mechanical behavior of either improved interfacial bonding or a modification of crystallinity. Heat treatment is a process where wood/fiber is exposed to elevated temperatures (150–280 °C) under controlled atmospheric conditions to improve properties such as reduced shrinkage, swelling, moisture content, enhanced decay resistance, and weather durability. However, it also leads to decreased mechanical properties, such as strength and stiffness. Biological methods could be cellulose modification either by microbial fermentation or by the incorporation of exogenous molecules, therefore offering a very effective chemical-free method for bacterial and plant cellulose fibers. These are scalable and quite effective methods [127,128]. With high efficiency and environmental friendliness, the biological process intends to establish bacterial cellulose (BC) functionalization methods through microbial fermentation. It uses glucose that is treated with 6-carboxyfluorescein (6CF-Glc) as a substrate. On this basis, it proposes alternative technologies for modifying bacterial cellulose as a substitute for chemical and physical agents.

Cellulose can also be modified chemically by methods such as phosphorylation [129], sulfonation [130], esterification [131], and etherification [132] to impart better properties. Other methods include amination [133], amidation [134], cationic polymerization [135], silylation [136], atom transfer radical polymerization (ATRP) [137], controlled polymerization [138], and ring opening metathesis polymerization (ROMP) [139]. The phosphorylation of microcrystalline cellulose (MCC) was achieved using phosphoric acid in the presence of molten urea, enhancing the material's adsorption properties by incorporating phosphate groups that increased reactivity and surface charge. Sulfonation was carried out by treating oxidized cellulose fibers with sodium bisulfite to convert some hydroxyl groups into sulfonic acid groups, which improved the ionic conductivity and selective transport property of the cellulose electrospun fibers. Cellulose nanofibers were esterified with toluene, sulfuric acid as a catalyst, and para-amino-benzoic acid under microwave irradiation and then passed through suction filter, washed with ethanol, and dried. In a one-pot

process, cellulose was etherified via a hydroxyl–yne click reaction, forming ether bonds that enhanced UV shielding, mechanical strength, and solvent resistance.



**Figure 2.** Classification of cellulose modification methods.

Cellulose was chemically modified by introducing amine groups through reactions with ethylenediamine to increase its total reactivity and network-forming ability in adhesives (known as aminated cellulose or aminated nanocellulose). Amidation was carried out by mixing hydroxy carboxymethyl cellulose (HCMC) with amines at 140 °C with rotary stirring for 20 h, followed by filtration, washing with a solvent, and drying to yield the amidated derivatives. In cationic polymerization, a cationic monomer such as diallyldimethylammonium chloride (DADMAC) was grafted in situ to cellulose fibers using a free radical initiator, increasing charge density and filler retention. Silylation was performed by treating CNCs with hexadecyltrimethoxysilane and perfluorooctyltriethoxysilane to improve hydrophobicity by replacing hydroxyl groups with lengthy chains of alkyl and fluoroalkyl, respectively. Using ATRP, thermo-responsive and fluorescent polymers can be grafted onto cellulose nanocrystals in a metal-free, light-mediated way exploiting 10-phenyl-phenothiazine (PTH) as a photocatalyst. Controlled polymerization allows for the determination of polymer molecular weight, graft length, and architecture so that the polymers may be accurately grafted to the cellulose during chemical modification. Grubbs' catalyst was used in ring-opening metathesis polymerization (ROMP) to graft polynorbornene onto cellulose fibers to increase hydrophobicity and change structural properties. These modifications increase the reactivity, conductivity, solubility, flexibility, and compatibility of cellulose, hence its applications in many electrochemical sensors.

### 3. Fabrication of Cellulose-Based Electrochemical Sensors

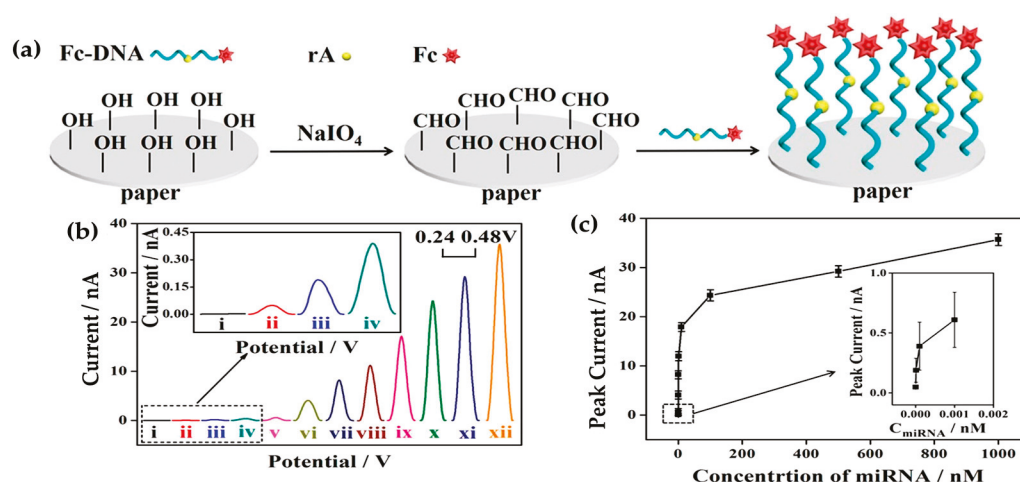
The technology behind sensing platforms has been developed in recent decades, resulting in the creation of robust systems for quick, simple, and cost-effective analysis [140]. This progress has paved the way for the rise of point-of-care testing, which focuses on quantifying various targets in body fluids for diagnostics and health monitoring [141–143]. Wearable sensors have emerged as an innovative approach for non-invasive biosensing, particularly for continuous health monitoring, even during exercise [144–148]. Different types of approaches have been employed to enhance cellulose-based electrochemical



sensors. Techniques originally introduced for paper-based sensors and nanocomposite fabrication have been applied to improve sensitivity. This has enabled the development of cellulose materials tailored for electrochemical detection.

### 3.1. Paper-Based Electrochemical Sensors

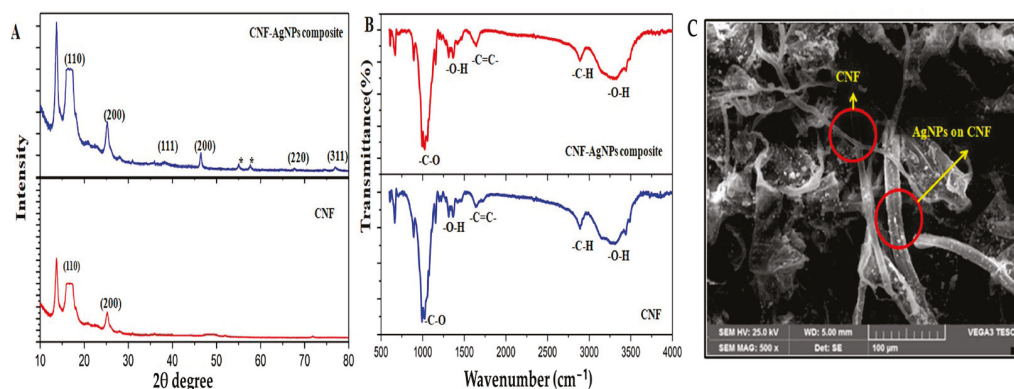
Carbon nanotubes and ferrocene-labeled DNA (Fc-DNA) were used to modify paper-based screen-printed electrodes for miRNA detection in serum samples (Figure 3) [149]. DNA immobilization on paper-modified electrodes enhances the reliability and responsiveness of bioassays, hence showing promise for point-of-care (POC) diagnostics. More recently, a composite paper has been fabricated via the traditional papermaking method using cellulose fibers (CFs) for conductivity and GO for electrocatalytic properties [150]. This approach can be efficiently scaled up to create affordable, high-quality, paper-based electrochemical sensors. The composite paper exhibited excellent stability and reproducibility in electrochemical properties with noticeable electrocatalytic activity [27].



**Figure 3.** Fabrication of a paper-based electrochemical sensing platform for miRNA: the immobilization of ferrocene-labeled DNA (Fc-DNA) on paper. (a) The detection of the lung cancer-specific biomarker miRNA-21 at different concentrations using differential pulse voltammetry. (b) DPV currents of the paper-based electrochemical sensor (PES) response to increasing miR-21 concentrations: (i–xii) 0,  $10^{-15}$ ,  $10^{-14}$ ,  $10^{-13}$ ,  $10^{-12}$ ,  $10^{-11}$ ,  $10^{-10}$ ,  $10^{-9}$ ,  $10^{-8}$ ,  $10^{-7}$ ,  $0.5 \times 10^{-7}$ , and  $10^{-6}$  M, respectively. (c) The corresponding calibration curve, with peak current plotted against miR-21 concentration. An inset shows the curve for lower miR-21 concentrations in a dotted square frame [149]. Copyrights: images have been taken with permission from © 2019, American Chemical Society.

### 3.2. Nanocellulose-Based Nanocomposite Electrochemical Sensors

Nanocellulose-based sensors were created by using cellulose nanofibers from sugarcane bagasse and silver nanoparticles (AgNPs). To create AgNPs, 1 mM silver nitrate was added to the cellulose nanofibers (CNFs). Ultrasonication was then applied, which helped the silver nanoparticles attach to the surface of the CNFs. CNF-AgNPs composite was then applied to modify a graphite electrode. The electrode was polished to a mirror finish, sonicated to remove any particles that were not tightly attached, and coated with a 5  $\mu\text{L}$  solution of the composite before being dried. The finished graphite/CNF-AgNPs sensor was stored at 4  $^{\circ}\text{C}$  and characterized using electrochemical techniques, including electrochemical impedance spectroscopy (EIS). This method effectively produced a nanocellulose-based composite electrode, which showed great potential for electrochemical sensing applications [151]. Figure 4 presents the structural analysis of the CNF-AgNPs composite.



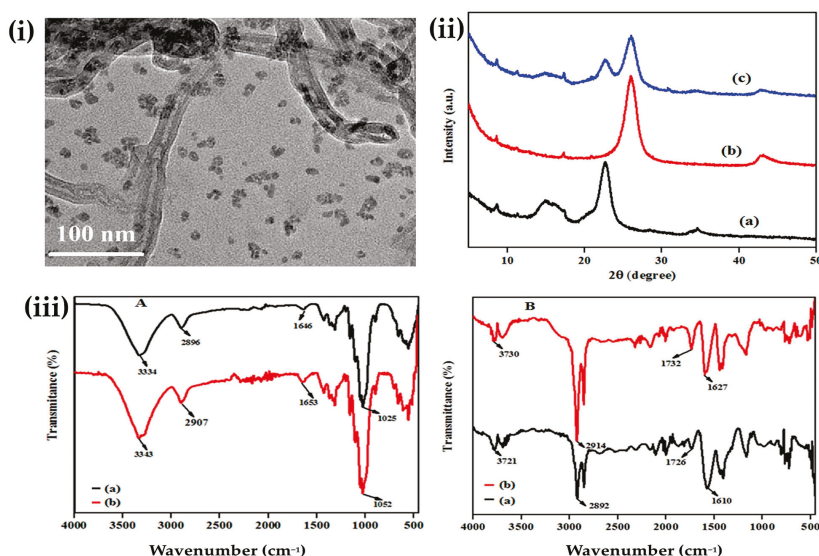
**Figure 4.** (A) XRD pattern showing the structure of CNF and the CNF-AgNPs composite. (B) FTIR spectrum comparing the CNF and CNF-AgNPs composite. (C) SEM image displaying the morphology of AgNPs and CNF [151]. Copyrights: images have been taken with permission from © 2021, Elsevier.

Shalauddin et al. developed a composite electrode using functionalized multi-walled carbon nanotubes (f-MWCNTs) and nanocellulose (NC) for the electrochemical detection of diclofenac sodium (DCF). F-MWCNTs were prepared by refluxing pristine MWCNTs in a mixture of nitric acid and sulfuric acid in a ratio of 1:3 for 24 h followed by washing and drying. The nanocellulose was prepared from cotton linter using acid hydrolysis with hydrochloric acid and sulfuric acid, and then it was centrifuged, washed, and dried. To modify the electrode, a glassy carbon electrode (GCE) was first polished and then sequentially coated with suspensions of NC and f-MWCNTs. The 5 mM NC solution was applied to the GCE and allowed to dry, and after then, 6 mM f-MWCNTs solution was dropped-cast onto it. The composite electrode was characterized using TEM, FTIR, and XRD to confirm the uniformity and surface structure. The final f-MWCNT/NC/GC electrode demonstrated enhanced electrical conductivity and a larger surface area, which significantly improved its ability to electrochemically detect DCF. To examine the electrochemical properties, cyclic voltammetry (CV), differential pulse voltammetry (DPV), and electrochemical impedance spectroscopy (EIS) were utilized [152]. Figure 5 illustrates the TEM image of NC/f-MWCNTs composite, XRD patterns of NC, f-MWCNTs, and NC/f-MWCNTs composites, and FTIR spectra of cellulose and nanocellulose, as well as pristine and f-MWCNTs.

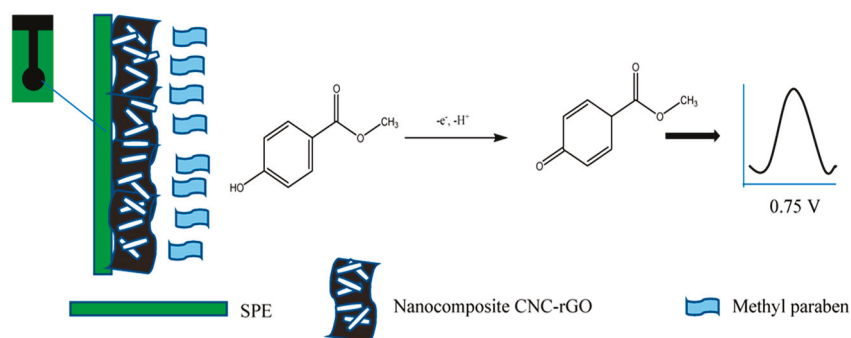
Cellulose nanocrystal–graphene electrochemical sensors were created by modifying electrodes with graphene or their derivatives, like reduced graphene oxide (rGO), and combining them with nanomaterials such as cellulose nanocrystals (CNC). The fabrication process starts by dispersing 1 mg of rGO in ethanol and 1 mg of CNC in deionized water, which are then mixed ultrasonically to form a stable nanocomposite. The composite is drop-coated onto the surface of a screen-printed electrode (SPE) and allowed to air dry at room temperature. To examine the electrochemical properties of both the bare and modified electrodes, methods such as cyclic voltammetry (CV), differential pulse voltammetry (DPV), and electrochemical impedance spectroscopy (EIS) are utilized. The scan rate, pH, and CNC:rGO composite ratios (ranging from 0.5:1 to 3:1) are adjusted to optimize the sensitivity for detecting analytes such as methyl paraben (MP). The sensor's performance is tested for reproducibility by measuring the current response of five different electrodes and for repeatability by continuously measuring a single electrode's response. Stability is checked by monitoring the current over a period of 28 days. The potential interference from substances like ascorbic acid, benzoic acid, salicylic acid, and citric acid is tested in mixed solutions. Lastly, the sensor is applied in real-world sample analysis, such as detecting MP in aloe vera cream using the standard addition method, which demonstrates



the practical use of the fabricated graphene-based electrochemical sensor [153]. Figure 6 shows a schematic representation of the sensor's fabrication process and its detection of MP.



**Figure 5.** (i) TEM image of the nanocellulose/f-MWCNTs composite. (ii) X-ray diffraction patterns of (a) nanocellulose, (b) f-MWCNTs, and (c) nanocellulose/f-MWCNTs composite. (iii) FTIR spectra of (A) cellulose and nanocellulose and (B) pristine and f-MWCNTs [152]. Copyrights: images have been taken with permission from © 2019, Elsevier.



**Figure 6.** A schematic representation of the sensor's fabrication process and its detection of MP [153]. Copyrights: images have been taken and reproduced from © 2019, MDPI.

## 4. Electrochemical Sensors

### 4.1. Medical and Healthcare Sensors

Microbial nanocellulose (MNC) and screen-printed carbon electrodes (SPCEs) are used to create a wearable sensor platform that can detect biomarkers and harmful metals in sweat in real time [154]. A peptide nucleic acid (PNA)-based electrochemical biosensor for the detection of *Mycobacterium tuberculosis* was designed on a screen-printed carbon electrode modified with  $\text{NH}_2$ -rGO/TEMPO-NCC nanohybrid films [155], and a selective cholesterol sensor was also developed using silylated graphene oxide-grafted chemically modified nanocellulose (Si-GO-g-CMNC) with zinc oxide (ZnO) to enhance conductivity [156]. For the determination of phenol, a biosensor was developed using the nanocrystalline cellulose (NCC)/CdS quantum dots (QDs) nanocomposite, which was modified with cetyltrimmonium bromide (CTAB) and 3-mercaptopropionic acid (3-MPA) for the immobilization of tyrosinase enzyme (Tyr). Its linear response to phenol was in the range from 5 to 40  $\mu\text{M}$ , while sensitivity and limit of detection (LOD) were estimated as 0.078  $\mu\text{A}/\mu\text{M}$  and 0.082  $\mu\text{M}$ , respectively [157].

A low-cost, reproducible glucose sensor using TEMPO-oxidized cellulose nanocrystals (CNCs) as a matrix was developed. The sensor showed a linear range of 0.1–2 mM, sensitivity of  $5.7 \pm 0.3 \mu\text{A cm}^{-2} \cdot \text{mM}^{-1}$ , and a detection limit of 0.004 mM. It maintained 92.3% of its initial response after 30 measurements and had a 1-month shelf life. The sensor was successfully used to monitor glucose consumption in fibroblast cell cultures [158]. A graphene paper functionalized with fractal platinum nanocauliflower was developed for the electrochemical biosensing of glucose and *E. coli* O157:H7. The sensor showed high sensitivity and detection limits for glucose and *E. coli*. It offered fast response times (6 s for glucose, 12 min for *E. coli*) and demonstrated potential for point-of-care biosensing applications [159]. A polypyrrole–cellulose nanocrystal (PPy-CNC) composite with glucose oxidase (GOx) was also developed for glucose sensing. The sensor showed high sensitivity and detection limit, and a range of 1.0–20 mM glucose. It excluded interfering substances and maintained over 95% of its initial response after 17 days, with good reproducibility and stability [160].

Interestingly, an ultrasensitive sandwich-type electrochemical immunosensor was constructed using graphene–perylene-3,4,9,10-tetracarboxylic acid–nanocellulose–Au nanocomposites to establish the detection platform of avian leukosis virus subgroup J (ALV-J), which displayed wide detectable ranges with low limits of detection. The prepared sensor was characterized by high sensitivity, selectivity, reproducibility, and stability, having good application prospects toward clinical ALV-J detection [161].

#### 4.2. Environmental Sensors

The development of a novel electrochemical sensor was presented for detecting  $\text{Hg}^{2+}$  in water, utilizing a hybrid nanocomposite of reduced graphene oxide (rGO), cellulose nanowhiskers (CNWs), and polyamide 6 (PA6) nanofibers. This sensor demonstrated enhanced charge transfer, high sensitivity, excellent stability, selectivity, a low detection limit, and a wide dynamic range for mercury detection [162]. Bacterial cellulose–gold nanoparticle (BC-AuNP) hybrid nanofibers were synthesized and used to create an electrochemical biosensor for hydroquinone detection. The sensor exhibited excellent electrocatalysis for dopamine, with a low detection limit of 5.71 nM and a wide linear range (30–100 nM). It showed good repeatability, selectivity, and stability and was successfully applied to detect hydroquinone in lake water samples [109]. The electrochemical behavior of atrazine (ATZ) was investigated in a Britton–Robinson buffer at pH 4.3 using a cellulose-modified pencil graphite electrode. Characterization of the sensor was carried out by electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV), presenting a reduction peak at 880 mV in CV. A linear response of ATZ was obtained in the range from 5.0 ng/mL to 320 ng/mL, with a detection limit of 0.008 ng/mL. The sensor was of high selectivity, sensitivity, and good reproducibility. It has been successfully applied in the detection of ATZ in drinking water, giving recoveries of 98.8–99.1% [163]. An electrochemical biosensor based on nanocellulose was developed to selectively and sensitively detect xanthine (XA) for fish spoilage monitoring. The nanocellulose, prepared from raw cotton, had xanthine oxidase immobilized onto it. This biosensor showed a linear range of detection between 3 and 50  $\mu\text{M}$ , while the limit of detection was 47.96 nM, and it was highly sensitive. Stability, after one month, was excellent, up to 97%, as well as high selectivity, which resulted in good agreement with commercial methods utilizing spectrophotometry [164]. Films of cellulose nanocrystals–polyaniline were developed as highly sensitive electrochemical sensors, responding to various kinds of stimuli. The incorporation of polyaniline (PANI) into the chiral nematic CNC films allowed for changes in color that depended on various environmental factors such as humidity, pH, and organic solvents. The incorporation of glucose enhanced the flexibility of these films without breaking the chiral structure.

These films demonstrated distinct color and conductivity changes depending on the conditions and, therefore, were good candidates for use in multi-sensing applications. A two-layer CNC-PANI film was also prepared for use as a conductive wire that completes a circuit upon stimulation and can find practical applications in environmental monitoring or reaction condition warnings [165]. Some examples of cellulose-based electrochemical sensors are described in Table 1 with materials, analytes, and detection methods such as amperometry, chronoamperometry, differential pulse voltammetry (DPV), square wave voltammetry (SW), electrochemical impedance spectroscopy (EIS), and cyclic voltammetry (CV), among others.

**Table 1.** List of cellulose-based electrochemical (Bio) sensors for the detection of varied analytes.

| Materials                                                                                                                                                   | Analytes                                                                                       | Method of Detection                                                | Reference |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------|
| Microbial nanocellulose (MNC)/screen-printed carbon electrodes (SPCEs)                                                                                      | Pb <sup>2+</sup> , Cd <sup>2+</sup> , uric acid, and 17 $\beta$ -estradiol in artificial sweat | DPV                                                                | [154]     |
| Reduced graphene oxide (NH <sub>2</sub> -rGO)/2,2,6,6-tetramethylpiperidin-1-yl) oxyl nanocrystalline cellulose (TEMPO-NCC)/screen-printed carbon electrode | Mycobacterium tuberculosis                                                                     | DPV, EIS, CV                                                       | [155]     |
| Silylated graphene oxide-grafted chemically modified nanocellulose (Si-GO-g-CMNC)/ZnO incorporated in CMNC/glassy carbon electrode                          | Cholesterol                                                                                    | CV, DPV                                                            | [156]     |
| NCC/CdS quantum dots (QDs)/cetyltrimmonium bromide (CTAB)/3-mercaptopropionic acid (3-MPA)/tyrosinase enzyme (Tyr)                                          | Phenol                                                                                         | DPV                                                                | [157]     |
| TEMPO-oxidized CNCs/glucose oxidase (GOx)/screen-printed electrode                                                                                          | Glucose                                                                                        | CV, chronoamperometry                                              | [158]     |
| Graphene paper/rGO/graphene oxide-coated nanocellulose/glucose oxidase (GOx)/RNA aptamer/chitosan                                                           | <i>E. coli</i> O157:H7, glucose                                                                | EIS, CV                                                            | [159]     |
| Polypyrrole–cellulose nanocrystal/GOx                                                                                                                       | Glucose                                                                                        | CV, DPV                                                            | [160]     |
| Graphene-perylene-3,4,9,10-tetracarboxylic acid nanocomposites (GR-PTCA)/nanocellulose–Au NP composites (NC-Au)/the alkaline phosphatase (ALP)              | Avian leukosis virus subgroup J (ALV-J)                                                        | CV, DPV                                                            | [161]     |
| Cellulose nanowhiskers (CNWs)/rGO/polyamide 6 (PA6) electrospun nanofibers                                                                                  | Hg <sup>2+</sup>                                                                               | CV                                                                 | [162]     |
| Cellulose/pencil graphite electrode                                                                                                                         | Atrazine (ATZ)                                                                                 | SWV, CV                                                            | [163]     |
| Nanocellulose/xanthine oxidase (XO)/glassy carbon electrode                                                                                                 | Xanthine (XA)                                                                                  | DPV, EIS                                                           | [164]     |
| CNCs/polyaniline (PANI)/glucose                                                                                                                             | Humidity, pH, organic solvents                                                                 | Stimuli-responsive CNC/PANI composite films, electrochromic device | [165]     |
| TEMPO-oxidized cellulose nanofibers-polyethyleneimine hybrids/single-walled carbon nanotubes (SWCNTs)                                                       | Tetracycline                                                                                   | CV, DPV                                                            | [166]     |
| Thioctic acid (TA)/dopamine-grafted cellulose nanofibers (DCNF)/Li+                                                                                         | Strain, conductivity                                                                           | Electrical conductivity measurement                                | [167]     |
| CNCs/polydopamine (PDA)/AuNPs/polyvinyl alcohol/lactate oxidase (LOx)                                                                                       | Lactate in sweat                                                                               | Lactate sweat sensor                                               | [168]     |
| Cellulose/KOH                                                                                                                                               | Hydroquinone, catechol                                                                         | CV, amperometry                                                    | [169]     |

Table 1. Cont.

| Materials                                                                                           | Analytes                       | Method of Detection                 | Reference |
|-----------------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------|-----------|
| Cellulose/polystyrene sulfonate sodium (PSS)                                                        | Ion concentration in sweat, pH | Cellulose-based conductive membrane | [170]     |
| Cellulose hydrogel/AgNPs/ferrocyanide redox probe                                                   | Sulfamethoxazole               | SWV                                 | [171]     |
| Cellulose nanofibers from wastepaper/1-(2-hydroxy-1-naphthylazo)-2-naphthol-4-sulfonic acid (HNNSA) | Co <sup>2+</sup>               | Cobalt nanosensor                   | [172]     |
| Cellulose/carbon nanotubes/glucose oxidase/Pt/Ag/AgCl                                               | Glucose                        | Continuous glucose sensor           | [173]     |

## 5. Challenges and Future Perspectives

As a result of the excellent properties of natural cellulose, such as being biocompatible, environmentally friendly, and versatile, cellulose-based electrochemical sensors offer an exciting alternative to state-of-the-art sensor technologies. These sensors have made striking progress in issues related to factors such as sensitivity and stability, thereby making them useful in various fields of possible applications like medical diagnostics, wearable technology, and environmental monitoring. However, several challenges persist in the full establishment of these sensors. Improvement in the quality of cellulose material is regarded as one of the main challenges. Indeed, the processes for the generation of high-quality nanocellulose are complicated and generally have low yields, hence raising difficulties for the elaboration of large-scale production routes. While such sensors demonstrate higher sensitivity in comparison with early types of sensors, further improvement in their selectivity and sensitivity to complex substances is still necessary for the satisfaction of a series of clinical and environmental demands. There is another issue: stability over time, because fouling, degradation, and environmental stress may impact sensor performance. Another problem is how to scale up production to make these sensors commercially viable while keeping costs low and performance consistent.

Some exciting possibilities soon will, therefore, be focused on the development of these sensors. Many other advanced nanomaterials, such as metal nanoparticles, will also be included in cellulose and may afford improved selectivity, stability, and sensitivity of the sensors toward a wide range of substances. Again, the sensors will be tailored for specific uses like medical diagnosis, environmental monitoring, and biosensing, keeping in view the requirements of the industry. The integration of such sensors with the Internet of Things (IoT) and artificial intelligence (AI) might enable the making of smart healthcare devices and real-time environmental monitoring systems. Furthermore, advances in manufacturing techniques are foreseen to allow for the optimization of such sensors regarding efficiency, scalability, and cost, thus enabling modern opportunities for their wide exploitation. Due to the eco-friendly nature of cellulose sensors and their potential for further improvement, they are poised to become at the forefront of sustainable, low-cost, high-performance sensing technologies. These sensors will further be able to revolutionize the sensing arena in several industries once duly developed.

## 6. Conclusions

In conclusion, due to their biocompatibility, environmental sustainability, and versatility, cellulose-based electrochemical sensors may provide a far broader range of potential applications than those of the predominant sensor types known today. These sensors have registered substantial improvements in the qualities of sensitivity, stability, and functionality, which have enabled them to be applied in medical diagnostics, environmental monitoring, and the wearable technology sectors. Nevertheless, optimization of cellulose

materials is still needed, while there is a need to further improve selectivity and sensitivity for complicated analytes, along with long-term stability regarding real-life conditions. In addition, scalability is one of the important factors that will enable the commercialization of these sensors in widespread applications. However, the future of cellulose-based electrochemical sensors looks bright, with further advances in nanomaterial integration, sensor design, and synthesis techniques. The further development of such sensors, mainly through the incorporation of the Internet of Things (IoT) and artificial intelligence (AI), could provide cost-effective smart health devices and real-time environmental monitoring systems. Further research and innovation could position cellulose-based sensors at the forefront of sensing technologies' future, offering an ecological and effective solution for a wide variety of applications.

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## Article

# Magnetic Porous Hydrogel-Enhanced Wearable Patch Sensor for Sweat Zinc Ion Monitoring

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**Abstract:** Wearable sensors for sweat trace metal monitoring have the challenges of effective sweat collection and the real-time recording of detection signals. The existing detection technologies are implemented by generating enough sweat through exercise, which makes detecting trace metals in sweat cumbersome. Generally, it takes around 20 min to obtain enough sweat, resulting in dallied and prolonged detection signals that cannot reflect the endogenous fluctuations of the body. To solve these problems, we prepared a multifunctional hydrogel as an electrolyte and combined it with a flexible patch electrode to realize real-time monitoring of sweat  $\text{Zn}^{2+}$ . Such hydrogel has magnetic and porous properties, and the porous structure of hydrogel enables a fast absorption of sweat, and the magnetic property of the addition of fabricated  $\text{Fe}_3\text{O}_4$  NPs not only improves the conductivity but also ensures the adjustable internal structures of the hydrogel. Such a sensing platform for sweat  $\text{Zn}^{2+}$  monitoring shows a satisfied linear relationship in the concentration range of 0.16–16  $\mu\text{g/mL}$  via differential pulsed anodic stripping voltammetry (DPASV) and successfully detects the sweat  $\text{Zn}^{2+}$  of four volunteers during exercise and resting, displaying a promising path for commercial application.

**Keywords:** magnetic porous hydrogel; uniform distribution; natural sweat detection; fast sweat collection; sweat trace metals

## 1. Introduction

Wearable sensors have broken out as an emerging technology in health monitoring and personal physiological management. These sensors could provide monitoring data in a non-invasive and continuous way, making them an invaluable tool for medical professionals and individuals [1–3]. Sweat is one of the parameters for monitoring body health, and wearable sensors for sweat analysis are particularly significant as they contain information about the body's metabolic indicators [4,5]. For instance, wearable sensors for detecting trace metals in sweat can reflect the health status of the body [6], since it is easy to see the loss of trace elements through excessive exercise and the diet. Therefore, it is crucial to promote the development of wearable trace metal detection in sweat.

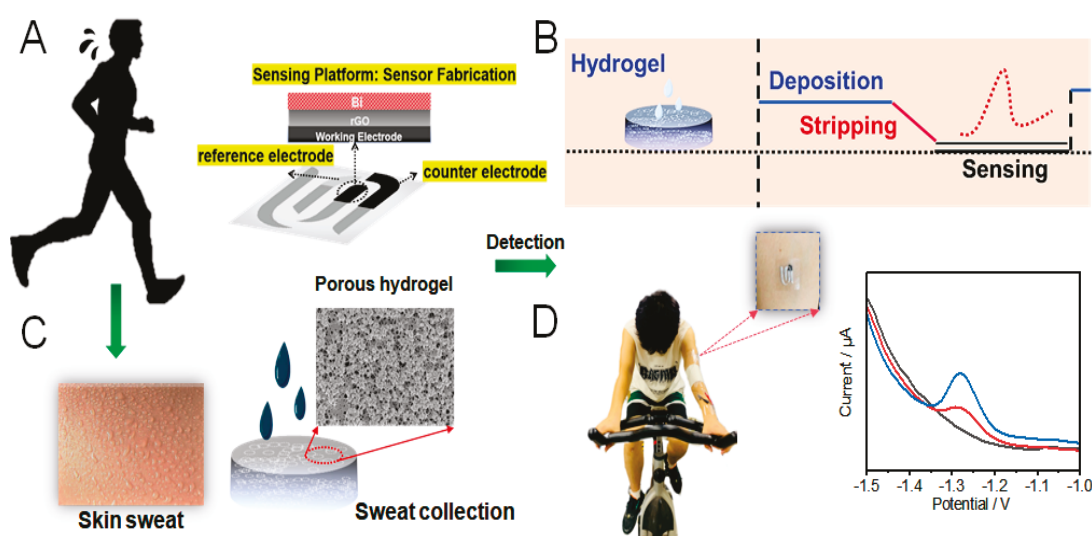
Zinc (Zn) is an essential trace element for life [7], which is required for most biological activities and processes in the human body, and is indispensable for the normal function of many enzymes, transcription factors, and replication factors. Chronic zinc deficiency can lead to hair loss, enteropathy dermatitis, and susceptibility to infections [8]. Even mild zinc deficiency can lead to clinically relevant symptoms that reflect multiple levels of organ dysfunction. When zinc deficiency is severe, both innate and adaptive immunity are severely suppressed, and patients may develop problems such as bullous dermatitis, diarrhea, hair loss, and intellectual disability [9]. Zn in normal human sweat ranges from 0.39 to 1.56  $\mu\text{g/mL}$ , reflecting physiological levels [8,10], and examining sweat for trace



metals could support the studies of toxicological and therapeutic aims. Therefore, sensitive analytical methods need to be developed to detect zinc ions in sweat.

Up to now, a few studies have been conducted on wearable sensors detecting sweat  $\text{Zn}^{2+}$ , including the wearable temporary tattoo sensor for the real-time monitoring of  $\text{Zn}^{2+}$ , displaying the acceptable limit of detection (LOD) for sweat  $\text{Zn}^{2+}$  detection [11]. The fabricated wearable microsensor array for simultaneous heavy metal monitoring in sweat shows an accurate and sensitive sensing platform with a temperature correction system [12]. However, those sensing platforms using long-term exercise for sweat collection to monitor the sweating of trace metals have the challenges of (a) long-term sweat collection prolonging the sensing of trace metals, where the real-time changes in sweat  $\text{Zn}^{2+}$  cannot be reflected, and (b), how, typically, the sweat-secretion process also involves the evaporation of sweat, leading to the accumulation of trace metals on the sensing surface and an inaccurate detection result. Therefore, it is necessary to build a sweat trace metal sensing platform with a fast and easy-going sweat collection system.

Herein, we introduce, for the first time, a multifunctional hydrogel with a porous, magnetically regulated structure and good conductivity introduced to the flexible patch sensing platform for detecting sweat  $\text{Zn}^{2+}$ . In Figure 1C, the sensing platform took advantage of the high porosity and capillary effect in a hydrogel that could achieve fast sweat collection [13,14], and the authenticity of the detection results were obtained. Compared with the reported work on sweat  $\text{Zn}^{2+}$  monitoring, our proposed sensing platform has a short sweating time and a favorable detection limit, reflecting our priority to make a user-friendly wearable patch sensor (Table S1). Additionally, as shown in Figure 1A,B, the typical electrochemical stripping voltametric determination of  $\text{Zn}^{2+}$  was performed, including the reduced Graphene Oxide (rGO) and bismuth (Bi) film-modified flexible patch electrodes for metal measurements [15–17]. The flexible electrode is prepared by the modification of a flexible polyurethane (PU) film as the substrate, showing good compactness with the printing stock [18]. As shown in Figure 1D, the flexible modified electrode patch was attached to the volunteer's forearm to monitor  $\text{Zn}^{2+}$ , and the porous and easily immobilized magnetic hydrogel could build a compatible sensing surface between the flexible electrode and the skin, making it user-friendly for monitoring  $\text{Zn}^{2+}$ , and achieving a good linearity in the range of 0.16–16  $\mu\text{g/mL}$ . On-body electrochemical measurements of sweat  $\text{Zn}^{2+}$  during routine activities (cycling and resting) on four recruited subjects are thus demonstrated by implementing our hydrogel-based flexible patch sensor stuck onto human skin.



**Figure 1.** (A) A schematic illustration of a flexible patch sensor with multifunctional hydrogel for the sensing of zinc ions ( $\text{Zn}^{2+}$ ) in sweat. (B) The electrochemical sensing procedure of sweat  $\text{Zn}^{2+}$  by DPASV. (C) Multifunctional hydrogel with a porous construction as a sweat reservoir. (D) Real-time monitoring of sweat  $\text{Zn}^{2+}$  during exercise with the flexible patch sensor stuck on a subject's forearm.

## 2. Materials and Methods

### 2.1. Materials

Agarose (Adamas-bate), GO (4 mg/mL, Carmery, Huzhou, China), aminated multi-wall carbon nanotubes (NH<sub>2</sub>-MWCNT, ~50  $\mu$ m, Aladdin, Shanghai, China), and Bi standard solution (Xiamen Standards Ltd., Xiamen, China) were used. CaCO<sub>3</sub> (600 mesh) were purchased from (Junhui Polymer Guangxi Technology Co., Ltd., Hezhou, China). FeCl<sub>2</sub>·4H<sub>2</sub>O (Hengxing Chemical Reagent Co., Ltd., Tianjin, China), MgSO<sub>4</sub>, PbC<sub>4</sub>H<sub>6</sub>O<sub>4</sub>·3H<sub>2</sub>O (General-Reagent, Shanghai, China), and CdCl<sub>2</sub> were purchased from Titan technology Co., Ltd. (Shanghai, China). CuSO<sub>4</sub>·5H<sub>2</sub>O and Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O were purchased from (Sinopharm Group Chemical Reagent Co., Ltd., Shanghai, China). Acetic acid (Jiangsu Qiangsheng Functional Chemical Co., Ltd., Changshu, China) was used. All the reagents were of analytical reagent grade. Elastic waterborne polyurethane (PU) film made of medical adhesive (HUAWEI breathable WPU film, Wuhan, China), polyethylene terephthalate (PET) (Dongsheng plastic material, Shenzhen, China), carbon ink (Inman Graphene Technology Jiangsu Co., Ltd., Huaian, China), silver ink (Shanghai Julong Electronic Technology Co., Ltd., Shanghai, China), and conductive fiber (Shenzhen Huizheng New Material Co., Ltd., Shenzhen, China) were also used.

### 2.2. Instruments

The electrochemical characterizations, including CV, DPASV, and impedance, were performed by using EmStat3 Blue (PalmSens, Houten, The Netherlands) and the CHI600E electrochemical station (CH Instruments, Inc., Shanghai, China). EIS was conducted at a frequency range of 0.01 Hz~100 kHz in 0.1 M KCl containing 5 mmol/L [Fe (CN)<sub>6</sub>]<sup>3−/4−</sup> solution. SEM images were collected on a JEM-2100F transmission electron microscope (200 kV accelerating voltage, Tokyo, Japan) with an energy dispersive spectrometer.

### 2.3. Preparation of the Fe<sub>3</sub>O<sub>4</sub> Nanoparticles

Synthesis of iron oxide nanoparticles (Fe<sub>3</sub>O<sub>4</sub> NPs): In accordance with a method in the previous literature [19], Fe<sub>3</sub>O<sub>4</sub> NPs were synthesized. In detail, 2.7 g ferric chloride hexahydrate (FeCl<sub>3</sub>·6H<sub>2</sub>O) was dissolved in 80mL glycol (EG) solution and dispersed by ultrasound to form a yellow solution. In addition, 2.0 g polyethylene glycol (PEG) and 7.2 g anhydrous sodium acetate (NaAc) were added to the mixture, and the solution quickly turned brown under intense agitation. After 30 min, the solution was transferred to a 100 mL sealed polytetrafluoroethylene-lined stainless-steel autoclave and reacted at 200 °C for 8 h. After the end of the reaction, it was taken out after natural cooling, and washed with water and ethanol in turn to clarify the top liquid. It was then dried in the oven at 60 °C and ground in a mortar to obtain the desired Fe<sub>3</sub>O<sub>4</sub> NPs.

### 2.4. Preparation of Multifunctional Hydrogels

The fabrication process of magnetic porous hydrogel was described as reported in our previous work [18]. Similarly, the agarose was used as a hydrogel template and the CaCO<sub>3</sub> (~23  $\mu$ m) as porogen. Agarose and CaCO<sub>3</sub> were first dissolved in DI water, with stirring and homogeneous mixing. Meanwhile, the NH<sub>2</sub>-MWCNT and Fe<sub>3</sub>O<sub>4</sub> NPs (~100 nm) in a weight ratio of (1:1) were mixed and added to the mixture of agarose and CaCO<sub>3</sub>, heating and stirring for 10 min at 95 °C. Then, the final mixture was added to a three-dimensional (3D) printed model (1 mm × 1 cm) to cure and achieve the uniformly sized hydrogels. During the curing process, a magnet is used to regulate the inner structures of agarose [20]. In detail, the magnet was placed above the hydrogel-coated 3D-printed model, and the cross-linked structure inside the hydrogel is evenly distributed through the action of the external magnetic field on Fe<sub>3</sub>O<sub>4</sub> NPs inside the hydrogel (Figure S2). Finally, the hydrochloric acid (HCl) solution was added to the fabricated hydrogels to obtain the porous structures of hydrogels [21].

### 2.5. Preparation of Electrochemical Sensing Platform

The flexible patch electrode was fabricated by using screen-printed technology, including the “SHNU” logo shape-based printed stencil designed by “Adobe Illustrator CS6” software. Commercial carbon ink and silver ink were used to print the three-electrode system. PU film was used as a flexible substrate with a printed working area, reference area, and counter area. In detail, the commercial silver ink was printed on a PU substrate through the designed stencil to define the reference electrode and connection area. Then, the printed electrodes were baked in the oven for 20 min at 80 °C, the carbon ink was printed on the working area and counting area, similarly, baking for 10 min at 80 °C. The proposed flexible patch electrode shows good resistance to mechanical deformation and good skin compactness at different statuses including bending and twisting (Figure S1).

The fabrication of the flexible electrochemical path sensing platform for the monitoring of sweat  $\text{Zn}^{2+}$  is displayed in Figure 1A. An amount of 4 mg/mL GO solution was used for the preparation of rGO at  $-1.2$  V for 400 s on the working electrode, after cleaning up the residual GO with DI water, followed by the deposition of Bi at  $-0.8$  V for 400 s, washing twice, and achieving the final flexible electrochemical sensing platform for sweat  $\text{Zn}^{2+}$ .

### 2.6. On-Body Test of Sweat $\text{Zn}^{2+}$ by Hydrogel-Based Flexible Patch Sensor

A total of 4 healthy volunteers (1 female and 3 males) were recruited. The flexible Zn patch sensor was stuck to a subject's forearm to monitor the  $\text{Zn}^{2+}$  concentration during exercising and resting (Figure 1D). Subjects were asked to ride a stationary cycle and sit on a chair for 8 min, respectively. Meanwhile, during the exercise and rest, along with the DPASV electrochemical method to detect sweat  $\text{Zn}^{2+}$ , all the sensing signals were recorded by an EmStat3 Blue. The DPASV parameters included the following: a pre-deposition voltage set at  $-1.4$  V, pre-deposition time of 8 min, and a voltage range applied from detection at  $-1.5$  to  $-0.8$  V vs. Ag/AgCl.

## 3. Results and Discussion

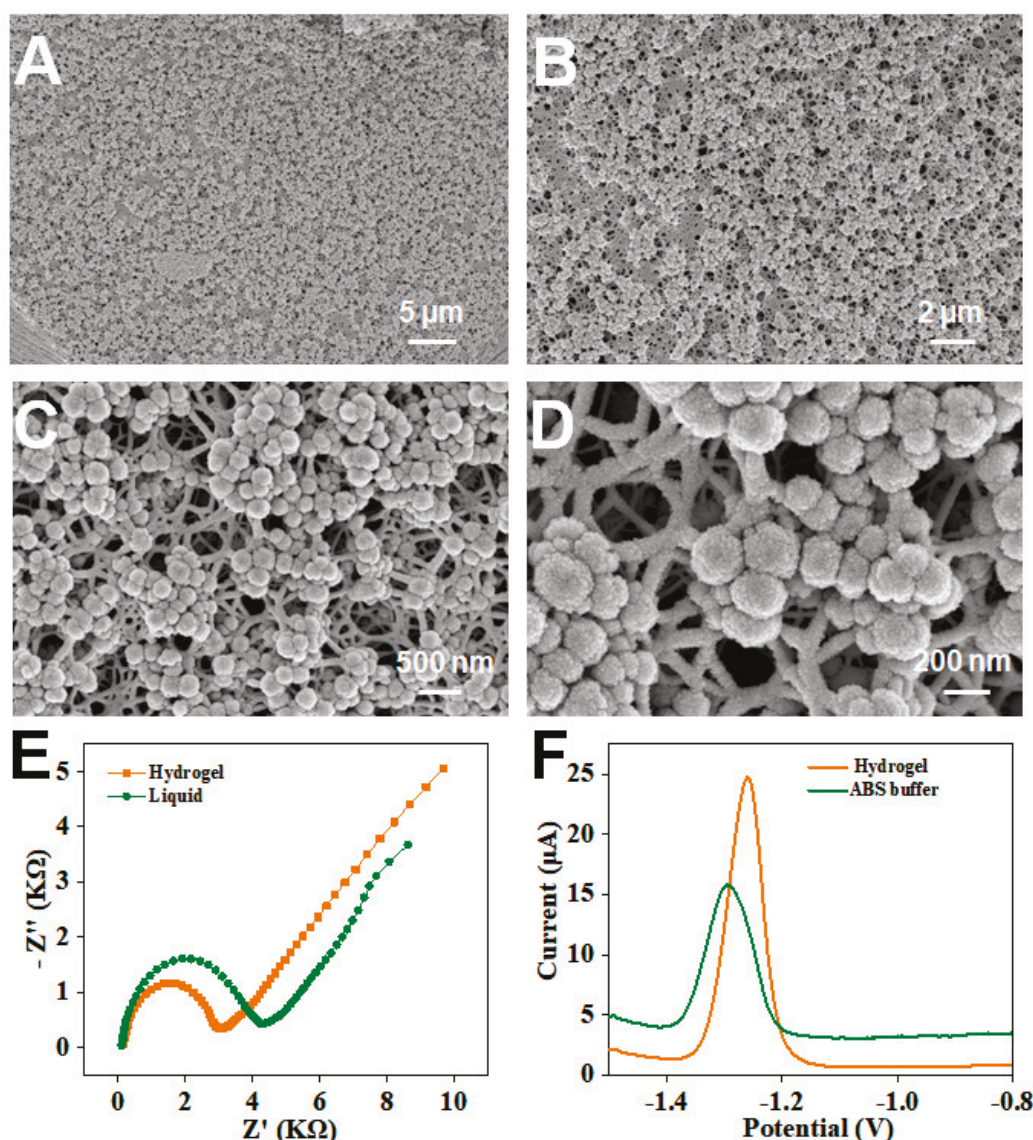
### 3.1. Uniform Structural Analysis of Magnetic Porous Hydrogel

The structure of magnetic porous hydrogels was investigated by Scanning Electron Microscopy (SEM). Figure 2A–D show SEM images of the magnetic porous hydrogel in the case of the acidic removal of  $\text{CaCO}_3$  particles. In Figure 2A, it can be seen from the SEM images of the cross-section of part of the gel that a large number of  $\text{Fe}_3\text{O}_4$  NPs are evenly distributed in the hydrogel. Additionally, in Figure 2B, the pores on the surfaces along with the  $\text{Fe}_3\text{O}_4$  NPs of the magnetic porous hydrogels are visible. The magnetic porous hydrogel, with the magnetically regulated structure formed under external magnetic induction, has evenly distributed pores on the surface. Figure 2C,D show the internal structure of magnetic porous hydrogel at magnification; after the magnetic regulation, the internal structure of the hydrogel was distributed in a network, cross-linking and arranged layer by layer; meanwhile, the  $\text{Fe}_3\text{O}_4$  NPs were evenly distributed in network structures, leading to the good conductivity of the hydrogel.

In addition, the electrochemical behavior of such hydrogel was investigated and compared with that of liquid electrolytes on electrodes. Electrochemical impedance spectroscopy (EIS) was used to evaluate the electrochemical properties of multifunctional hydrogels, including for ion exchange and charge transfer. The magnetic porous hydrogel was attached to the flexible electrode for electrochemical tests. EIS curves for magnetic porous hydrogels and electrolyte solution in the frequency range of 1 Hz to 100 kHz, acquired by soaking in a 0.1 M KCl solution containing 5 mmol/L  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  are displayed in Figure 2E. Low-frequency regions of the Nyquist plots reflect the diffusion defect of electrolyte ions in hydrogels [22]. The diffusion resistance of magnetic porous hydrogels of Figure 2E showed a relative reduction compared to the EIS results recorded on liquid electrolyte, demonstrating the fabricated magnetic porous hydrogel has good electron transfer properties and conductivity. Meanwhile, the feasibility of the rGO/Bi sensing system for detecting  $\text{Zn}^{2+}$  was further investigated in Figure 2F. From the compari-



son between hydrogel and the ABS (4.5) buffer-built sensing system, the hydrogel showed an increased sensing signal for  $\text{Zn}^{2+}$  at the concentration of  $1 \mu\text{g/mL}$  when measured by DPASV.

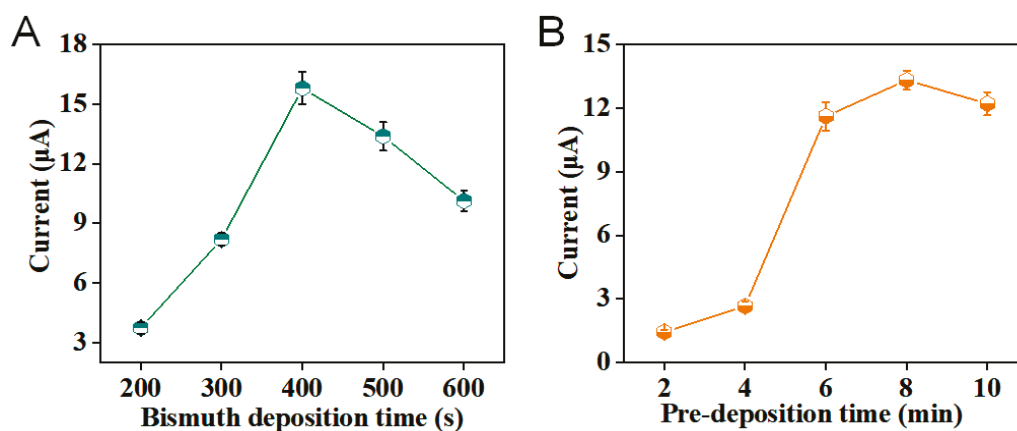


**Figure 2.** The scanning electron microscope (SEM) images of multifunctional hydrogel. (A,B) show the different magnifications of the cross-section of the magnetic porous hydrogel. (C) The cross-linked network structure of the hydrogel. (D) The uniform  $\text{Fe}_3\text{O}_4$  nanoparticles distributed in a hydrogel network structure. (E) The impedance of multifunctional hydrogel soaked in 5 mmol/L Ferro/ferricyanide and 0.1 mol/L KCl solution (impedance solution) and impedance solution. (F) The electrochemical detection of  $1 \mu\text{g/mL}$   $\text{Zn}^{2+}$  by DPASV in acetate buffer (ABS buffer, pH 4.5)-soaked multifunctional hydrogel and ABS buffer, respectively.

### 3.2. Optimization of rGO/Bi Film Sensing Platform

To realize the preferable electrochemical signals for the detection of sweat  $\text{Zn}^{2+}$  by DPASV, the deposition time of fabricated Bi film on the sensing electrode was surveyed. In Figure 3A, the optimal time was 400 s. Moreover, the electrochemical parameter of pre-deposition time for detecting  $\text{Zn}^{2+}$  by DPASV was investigated. As shown in Figure 3B, the optimal pre-deposition time was set at 8 min, achieving the highest current signal of  $\text{Zn}^{2+}$ . All the optimization surveys were implemented by using the hydrogel-based flexible patch sensor after deposition of rGO at  $-1.2 \text{ V}$  and Bi at  $-0.8 \text{ V}$  on the electrode [18]

by a PalmSense® small electrochemical system with a bluetooth accessory (Houten, The Netherlands). The DPASV electrochemical technique was applied to detect 1  $\mu\text{g/mL}$   $\text{Zn}^{2+}$  solution.



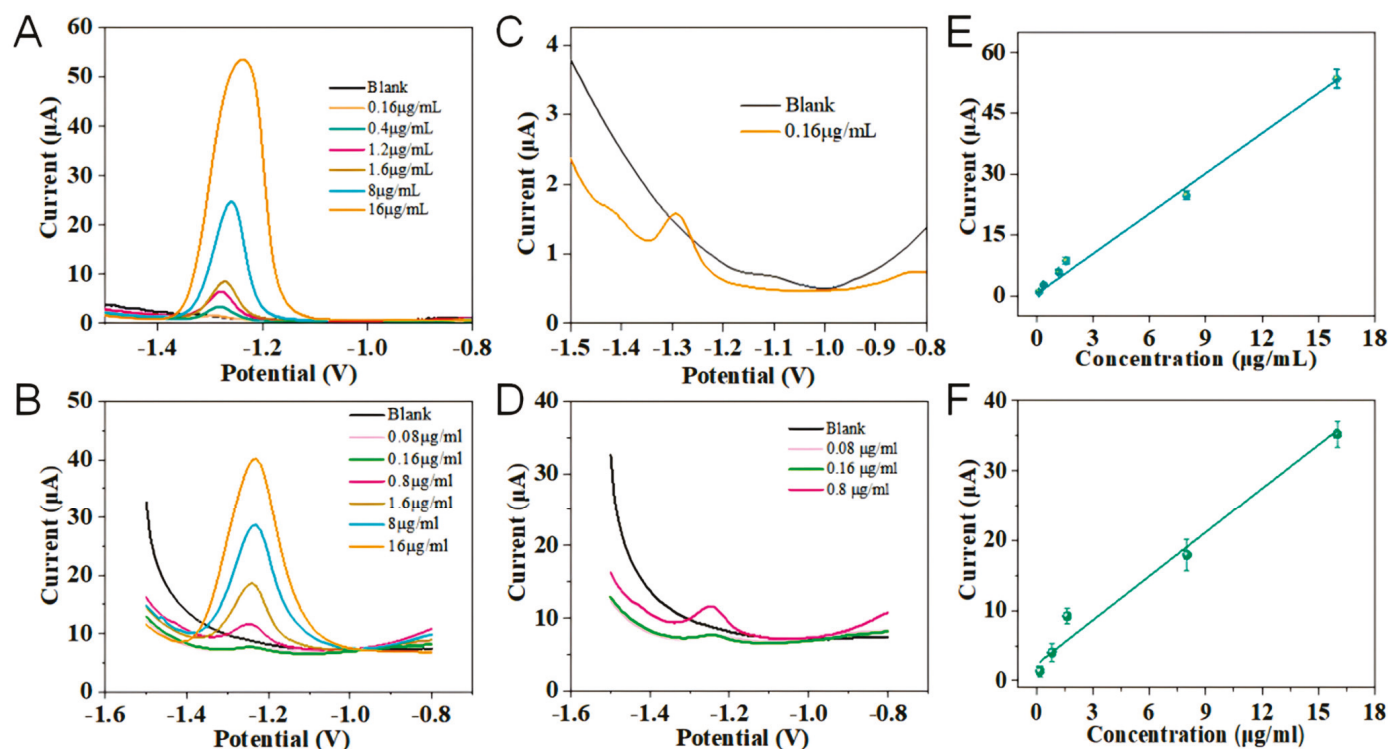
**Figure 3.** The optimization characterization of (A) the deposition time of bismuth (Bi) standard solution for the fabrication of Bi film in a sensing platform. (B) The pre-concentration time of  $\text{Zn}^{2+}$ . The DPASV strategy was applied with hydrogels soaked in 1  $\mu\text{g/mL}$   $\text{Zn}^{2+}$  ABS buffer.

### 3.3. rGO/Bi Film Flexible Patch Sensor for $\text{Zn}^{2+}$ Sensing

Based on the above observation, the magnetic porous hydrogel used as a solid electrolyte and a sweat reservoir with a magnetically regulated structure has excellent electrochemical performance, implementing a fast and effective sweat collection. As indicated in Figure 4A,D, the fabricated hydrogel was used on the flexible patch sensor with a small magnet under the patch to fix the hydrogel and achieve the stable sensing platform, observing the concentration-dependent DPASV response to  $\text{Zn}^{2+}$  with the hydrogel containing the HAC-NaAC (pH 4.5) buffer (Figure 4A) and artificial sweat (Figure 4D). Figure 4B,E show the low-concentration signal curves of  $\text{Zn}^{2+}$ . For each test, 4  $\mu\text{L}$   $\text{Zn}^{2+}$  solution with a certain concentration was added to the hydrogel. Clearly, Figure 4C,F show a similar wide linear relationship for detecting  $\text{Zn}^{2+}$ , ranging from 0.16  $\mu\text{g/mL}$  to 16  $\mu\text{g/mL}$  with the hydrogel-based flexible patch sensor. The resulting current response depended on the  $\text{Zn}^{2+}$  concentration, following the regression equations of  $I_{\text{buffer}} = 0.3653 + 3.3097C$  ( $\mu\text{g/mL}$ ),  $R^2 = 0.9641$  ( $n = 3$ ), and  $I_{\text{sweat}} = 2.362 + 2.089C$  ( $\mu\text{g/mL}$ ),  $R^2 = 0.9641$  ( $n = 3$ ). The result shows that the prepared hydrogel-based flexible patch sensor for  $\text{Zn}^{2+}$  detection has the satisfied detection limit and could directly detect  $\text{Zn}^{2+}$  in sweat.

### 3.4. Interference

The possible interfering ions with a concentration of 10  $\mu\text{g/mL}$ , such as  $\text{Pb}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Cd}^{2+}$ , and  $\text{Fe}^{2+}$ , were studied by using a magnetic porous hydrogel-based flexible patch sensor. As shown in Figure 5, the hydrogel-based sensing platform exhibits good detection selectivity for  $\text{Zn}^{2+}$  at the concentration of 1  $\mu\text{g/mL}$ . In all, the as-prepared hydrogel as a solid electrolyte possesses better electrochemical properties than liquid electrolytes. Because of the hydrogel having the arrangement of its inner structure regulated by an external magnet, the diffusion speed of  $\text{Zn}^{2+}$  ions to the surface of the electrode were enhanced, resulting in a favorable DPASV response.



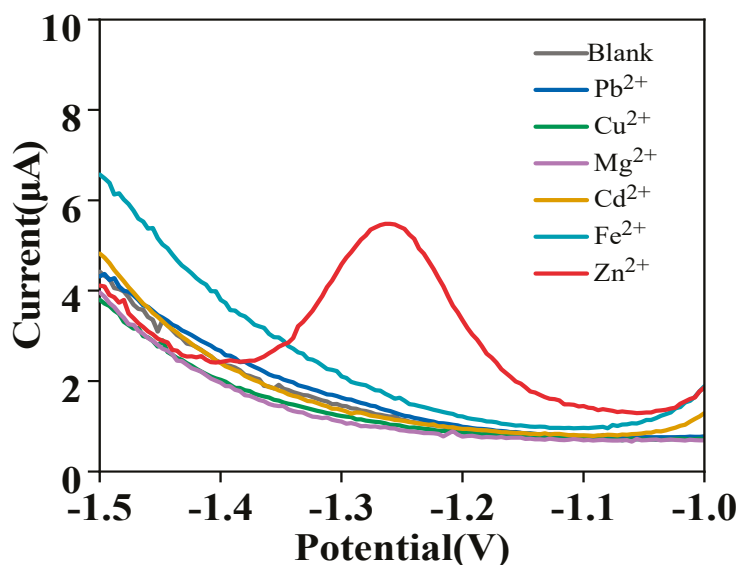
**Figure 4.** The concentration-dependent DPASV detection of  $Zn^{2+}$  using the flexible patch sensor installed with a hydrogel that soaked in 0.1 mol/L ABS buffer solution (A) and a hydrogel that soaked in artificial sweat (B). The zoomed-in low-concentration detection curves of  $Zn^{2+}$  in hydrogel with a 0.1 mol/L ABS buffer solution (C) and artificial sweat (D). The corresponding concentration linear dynamic plots of  $Zn^{2+}$  were obtained in the hydrogel with ABS buffer solution (E) and artificial sweat (F), respectively. The DPASV experimental conditions were as follows: pre-deposition voltage:  $-1.4$  V; voltage ranged from  $-1.5$  V to  $-0.8$  V vs. Ag/AgCl.

### 3.5. On-Body Characterization of Flexible $Zn^{2+}$ Patch Sensor

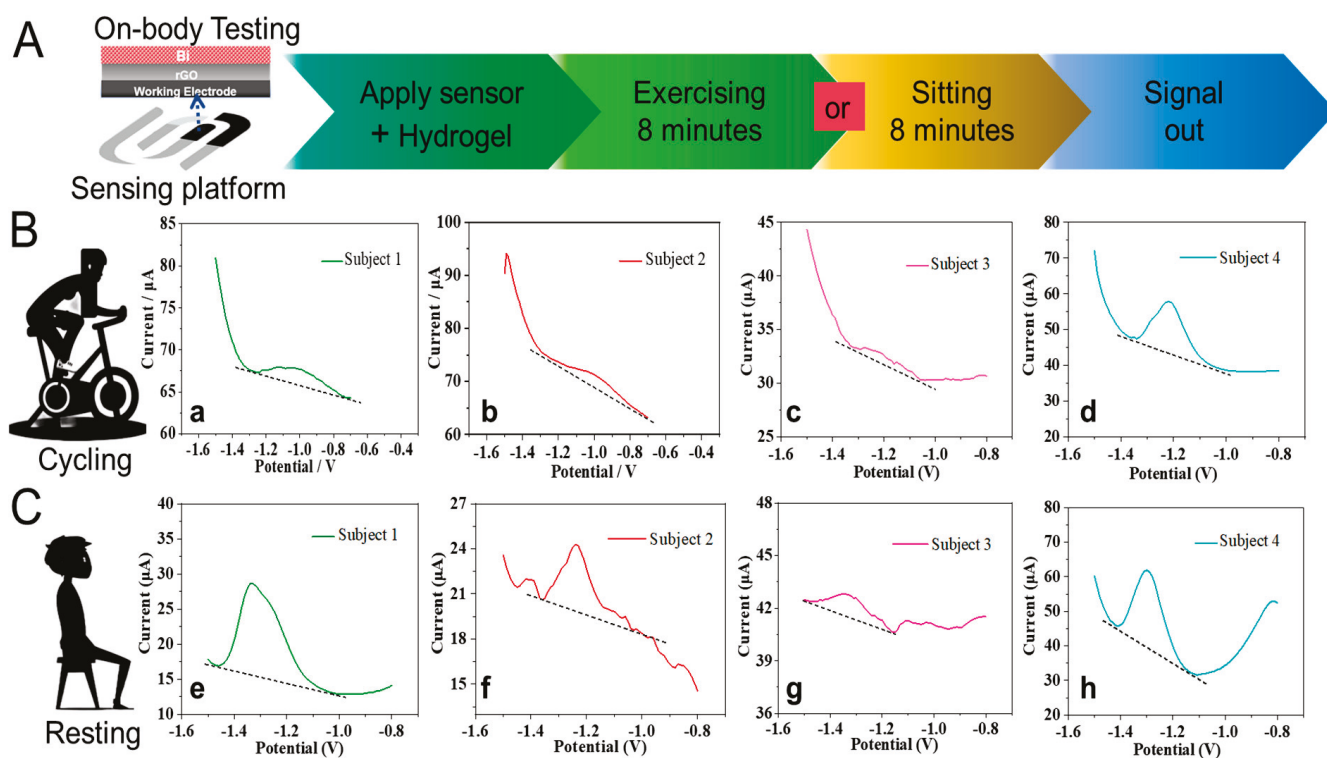
The on-body testing performance of the hydrogel-based flexible patch sensor was evaluated during routine activities (cycling and resting). The flexible patch sensor with hydrogel was stuck to the forearms of the participants (Figure 1D). In Figure 6A, the details of the on-body testing process were implemented by cycling (8 min) and resting (8 min), then recording the current signals. During the cycling test, the pre-concentration procedure was carried out along with the cycling for 8 min by volunteers. The prepared hydrogel with a porous structure could generate the electrochemical cell that established a fast sweat  $Zn^{2+}$  sensing platform. As shown in Figure 6B(a–d), the detection signals of  $Zn^{2+}$  from four subjects displayed stable background currents and stripping peaks. This indicates that the flexible patch sensor shows a reliable and stable sensing system even in cycling. In addition, the sweat  $Zn^{2+}$  of four subjects during the resting state has been investigated. As shown in Figure 6C(e–h), the four subjects keep sitting, and the flexible patch sensors stick to the subject's forearm; then, using the DPASV method, pre-concentration was performed for 8 min, recording the sensing signals. Nevertheless, from the comparison of the recorded sensing signals between Figure 6B,C, the sensing signals of sweat  $Zn^{2+}$  at the resting state were higher than those in the cycling state. This is due to how sweating at rest involves secretion at much lower rates than during exercise [23,24], which to some extent leads to the different  $Zn^{2+}$  concentrations in hydrogel during exercising and sitting, as well as the sensing signals. As reported, low secretion rates of resting sweat and evaporation are challenging for sweat collection [23]. However, the proposed hydrogel-based sensing platform for monitoring  $Zn^{2+}$  shows the favorable sensing of signals during



resting, indicating fast and effective sweat collection by hydrogel, leading to a rapid and accurate sweat  $\text{Zn}^{2+}$  sensing system.



**Figure 5.** The interference for the flexible patch sensor was studied by detecting interfering ions with a concentration of 10  $\mu\text{g/mL}$ , including  $\text{Pb}$ ,  $\text{Cu}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Fe}^{2+}$ , and a mixture with 1  $\mu\text{g/mL}$   $\text{Zn}^{2+}$ , respectively.



**Figure 6.** The strategy for sensing sweat  $\text{Zn}^{2+}$  on a hydrogel-based flexible patch sensor during routine activities (cycling and resting). (A) The modification and sensing process of on-body testing. (B) The flexible patch sensor for the detection of sweat  $\text{Zn}^{2+}$  of (a) male Subject 1, (b) male Subject 2, (c) male Subject 3, and (d) female Subject 4 during cycling. (C) The flexible patch sensor for the detection of sweat  $\text{Zn}^{2+}$  of (e) male Subject 1, (f) male Subject 2, (g) male Subject 3, and (h) female Subject 4 during sitting. The sweat  $\text{Zn}^{2+}$  on-body experimental conditions were as follows: pre-deposition voltage:  $-1.4\text{ V}$ ; the voltage ranged from  $-1.5\text{ V}$  to  $-0.8\text{ V}$  vs.  $\text{Ag/AgCl}$ .

Due to differences in daily diet, medication, and environmental effects, the sweat  $\text{Zn}^{2+}$  of subjects displayed signals at different levels. However, these results show well-defined  $\text{Zn}^{2+}$  stripping peaks around  $-1.3$  V, indicating that the flexible Zn patch sensor can successfully detect the presence of  $\text{Zn}^{2+}$  in sweat during routine activities. In particular, the sensing strategy of natural sweat  $\text{Zn}^{2+}$  was successfully detected under a resting state, which could reflect more realistic fluctuations of  $\text{Zn}^{2+}$  in the subjects' bodies [25,26], making it more user-friendly. In addition, the quantitative analysis of sweat  $\text{Zn}^{2+}$  was also studied by the standard additions of the collected sweat sample from Subject 3 (Figure S3) [11]. Consequently, the hydrogel-based flexible patch sensor displays good sensitivity and feasibility of application for sweat  $\text{Zn}^{2+}$  monitoring.

#### 4. Conclusions

In summary, we came up with an effective sensing strategy, for the first time using the fabricated magnetic porous hydrogel to collect sweat and generate the sweat reservoir on the sensing electrode to realize the detection of sweat  $\text{Zn}^{2+}$ . The prepared hydrogel consists of magnetic  $\text{Fe}_3\text{O}_4$  NPs and  $\text{NH}_2$ -MWCNT to achieve an acceptable conductivity. Additionally, the  $\text{CaCO}_3$  as a pore-forming agent was added to hydrogel to generate the porous structure of hydrogel by acid etching. Notably, the hydrogel exhibits a homogeneous distribution of its inner structure due to the magnetic regulation of an external magnet during the curing process. Such hydrogel-based flexible patch sensors with good conductivity and absorptive properties were successfully applied to the on-body evaluation of sweat  $\text{Zn}^{2+}$  ions of four subjects. The uniform distribution of  $\text{Fe}_3\text{O}_4$  NPs and porous hydrogels has increased absorption capability and electrolyte diffusion. As a result, the fabrication and implementation of the novel magnetic composite hydrogel as a solid electrolyte for sweat  $\text{Zn}^{2+}$  sensing has promising applications in real-time sweat monitoring.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/s24175627/s1>, Figure S1: the images of the flexible patch electrode; Figure S2: the synthetic details of the magnetic hydrogel; Figure S3: the quantitative analysis of sweat  $\text{Zn}^{2+}$  by the proposed method and ICP; Table S1: the comparable literature for the detection of sweat  $\text{Zn}^{2+}$  by wearable sensor.

**Author Contributions:** Conceptualization, W.T. and Y.C. (Yao Chu); methodology, W.T. and Y.C. (Yao Chu); software, W.T., Y.C. (Yao Chu), Y.C. (Yangyang Chen) and Z.L.; validation, Y.C. (Yao Chu), Z.L., Y.C. (Yangyang Chen), K.L., Y.S. and K.J.; formal analysis, Y.C. (Yao Chu), Z.L., Y.C. (Yangyang Chen), K.L., Y.S. and K.J.; investigation, W.T., Y.C. (Yao Chu); Y.C. (Yangyang Chen), and K.L.; resources, W.T. and H.Y.; data curation, W.T. and Y.C. (Yao Chu); writing—original draft preparation, Y.C. (Yao Chu); writing—review and editing, W.T.; visualization, W.T. and Y.C. (Yao Chu); supervision, W.T., Y.C. (Yao Chu), Y.C. (Yangyang Chen), Z.L. and K.L.; project administration, W.T., Y.C. (Yao Chu), Y.C. (Yangyang Chen), Z.L. and K.L.; funding acquisition, W.T. and H.Y. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** All subjects gave their informed consent for inclusion before they participated in this study. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Shanghai Normal University (2024(112)).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data will be made available upon request.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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## Article

# All-Fiber Flexible Electrochemical Sensor for Wearable Glucose Monitoring

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**Abstract:** Wearable sensors, specifically microneedle sensors based on electrochemical methods, have expanded extensively with recent technological advances. Today's wearable electrochemical sensors present specific challenges: they show significant modulus disparities with skin tissue, implying possible discomfort in vivo, especially over extended wear periods or on sensitive skin areas. The sensors, primarily based on polyethylene terephthalate (PET) or polyimide (PI) substrates, might also cause pressure or unease during insertion due to the skin's irregular deformation. To address these constraints, we developed an innovative, wearable, all-fiber-structured electrochemical sensor. Our composite sensor incorporates polyurethane (PU) fibers prepared via electrospinning as electrode substrates to achieve excellent adaptability. Electrospun PU nanofiber films with gold layers shaped via thermal evaporation are used as base electrodes with exemplary conductivity and electrochemical catalytic attributes. To achieve glucose monitoring, gold nanofibers functionalized by gold nanoflakes (AuNFs) and glucose oxidase (GOx) serve as the working electrode, while Pt nanofibers and Ag/AgCl nanofibers serve as the counter and reference electrode. The acrylamide-sodium alginate double-network hydrogel synthesized on electrospun PU fibers serves as the adhesive and substance-transferring layer between the electrodes. The all-fiber electrochemical sensor is assembled layer-by-layer to form a robust structure. Given the stretchability of PU nanofibers coupled with a high specific surface area, the manufactured porous microneedle glucose sensor exhibits enhanced stretchability, superior sensitivity at  $31.94 \mu\text{A} (\text{lg}(\text{mM}))^{-1} \text{cm}^{-2}$ , a broad detection range (1–30 mM), and a significantly low detection limit (1 mM, S/N = 3), as well as satisfactory biocompatibility. Therefore, the novel electrochemical microneedle design is well-suited for wearable or even implantable continuous monitoring applications, thereby showing promising significant potential within the global arena of wearable medical technology.

**Keywords:** all-fiber; electrospinning; electrochemical sensor; glucose continuous monitoring

## 1. Introduction

Accompanied by the development of wearable sensors and flexible material preparation technology, wearable monitoring methods based on electrochemical and optical sensors have substantially advanced [1–4]. However, due to the complexity of the SERS-based optical system, it is not easy to achieve portable detection, and commercial optical wearable devices cannot provide high precision compared with electrochemical sensors. Wearable electrochemical glucose detection has been extensively developed for use within the scope of laboratories and commercial products [5–9]. Gao Wei et al. have prepared a flexible skin patch sensing system by exploiting micro-nanofabrication techniques [10]. Joseph Wang and his team have leveraged 3D printing technology to create a wearable

microneedle array sensor capable of concurrently monitoring multiple physiological indicators [11]. Additionally, corporations such as Abbott and Dexcom have introduced continuous glucose monitoring (CGM) products that can continuously monitor glucose levels in the interstitial fluid (ISF), thereby providing a representation of blood glucose levels [12].

However, the wearable system designs mentioned above still have some issues that need to be resolved to improve the systems' monitoring capabilities in non-laboratory environments. For example, patch electrodes based on micro/nano fabrication methods have high requirements for the preparation method, and implantable commercial sensors based on hard microneedles can cause skin reactions after implantation due to the rigid PET substrate used [13]. To resolve these issues, researchers need a simple method of preparing electrodes that can conform to skin tissue deformation making them flexible for electrochemical use. Electrospinning technology is a simple method of preparing high-elasticity nanofiber films with high specific surface areas to obtain wearable and implantable electrochemical electrodes [14].

In this paper, we have designed an all-fiber wearable glucose sensor prepared by an electrospinning process. Using thermal evaporation, we prepared a dense gold film on PU mesh constructed by electrospinning, achieving good conductivity. Additionally, AuNFs were deposited on the working electrode to enhance the electrochemical activity of the electrode. The AuNFs, in conjunction with the PU electrospun fiber's porous mesh structure, provide abundant active sites for electrode reactions. The optimal concentration of AuNFs was determined to optimize the effective active area of the electrode. Moreover, modifying the electrode with Prussian Blue (PB) as a mediator for electron transfer in the enzyme reaction significantly reduced the potential applied on the electrode, enhancing electrode stability and reducing interference [15]. The electrodes' surface morphology and electrochemical performance were characterized using scanning electron microscope (SEM), cyclic voltammetry, and electrochemical impedance spectroscopy (EIS). In the layer-by-layer assembly process of the electrode, a double network hydrogel based on acrylamide and sodium alginate, reinforced by the electrospun mesh, was introduced to serve as an adhesive and a substance-transferring layer between the electrodes. Furthermore, due to the flexibility of the electrospun film, the wearable sensor system can maintain stable conductivity while conforming to skin deformation. The biocompatibility of the electrode was also evaluated, and a high degree of biocompatibility was observed, further proving its potential for practical applications. The sensor proposed in this study can advance research in wearable glucose detection and promote the development of wearable sensors.

## 2. Materials and Methods

### 2.1. Materials

The PU solution was prepared by mixing PU particles (Tecoflex SG-85A, Shanghai, China) and N, N-dimethylformamide (from Aladdin, Shanghai, China), and Tetrahydrofuran (from Adamas, Shanghai, China) at a weight ratio of 15:42.5:42.5 before magnetic stirring for 3 h at 55 °C to form a homogeneous transparent bubble-free solution. The PU is chemically pure, and tetrahydrofuran and dimethyl formamide are anhydrous. The acrylamide and sodium alginate, gold (III) chloride trihydrate and tetramethyl-ethylenediamine iron (III) chloride, potassium chloride, potassium ferricyanide (III), hydrochloric acid, GOx, Au nanoparticle (AuNPs), chitosan, glutaric dialdehyde, Nafion, uric acid (UA), ascorbic acid (AA) were purchased from Sigma-Aldrich, Shanghai, China. The N, N-methylene bisacrylamide, and ammonium persulfate were purchased from Adamas. The calcium carbonate nanopowder was purchased from Zkynxc (Beijing, China). Dulbecco's Modified Eagle Medium, 0.25% trypsin-EDTA, fetal bovine serum, human skin fibroblasts HSF T25, and phosphate-buffered saline (PBS) solution were purchased from Gibco, Shanghai, China. Penicillin-Streptomycin (100×) was purchased from TransGen, Beijing, China. A Live/Dead Cell Double Staining Kit and NucBlue Live Ready Probes were purchased from Invitrogen, Shanghai, China.



## 2.2. Fabrication of PU Nanomesh and Au Nanomesh and Pt/Au Nanomesh and Ag/AgCl/Au Nanomesh

The electrospinning PU solution was mentioned above. The prepared solution was added into a 10 mL plastic syringe using a 26G needle. The electrospun PU mesh was collected using a metallic roller with aluminum foil as the collector. During the electrospinning procedure, the applied voltage, electrospinning time, distance between needle and collector, spinning rate of collector, and pump rate were 15 kV, 150 min, 20 cm, 100 rpm, and  $0.2 \text{ mm min}^{-1}$ , respectively. Subsequently, we removed the electrospun film from the foil using a PET frame and placed the frame on a flat silicon wafer using double-sided adhesive. First, to obtain Au/PU nanomesh, a layer of Au film with a thickness of 100 nm was thermally evaporated onto one side of the PU mesh servers as the working electrode. To increase the stability of our electrode, a 100 nm Pt layer and a Ag layer were thermally evaporated on the Au/PU nanomesh. The Pt/PU nanomesh was used as the counter electrode. The Ag/AgCl/Au/PU electrode was obtained by immersing the Ag/Au/PU nanomesh into the 0.1 M  $\text{FeCl}_3$  for 1 min to prepare the reference electrode.

## 2.3. Optimization and Functionalization of Electrode

After the thermal evaporation of Au, this original Au working electrode was further optimized by electrodeposited AuNFs. AuNFs were electrodeposited in situ by cyclic voltammetry from  $-1 \text{ V}$  to  $0 \text{ V}$  (versus Ag/AgCl) for 20 cycles at the scan rate of  $0.02 \text{ V s}^{-1}$  in solution with  $\text{HAuCl}_4$  and phosphate buffer on the working electrode with a Pt electrode and Ag/AgCl electrode as counter and reference electrode, respectively. The concentration of  $\text{HAuCl}_4$  was investigated to determine the optimal electrochemical performance. The AuNFs/Au/PU electrode was further functionalized to fulfill the need to monitor glucose. First, a layer of PB was electrodeposited on the working electrode by cyclic voltammetry from  $0.5 \text{ V}$  to  $1.1 \text{ V}$  for 20 cycles at  $0.02 \text{ V s}^{-1}$  in the solution with 2.5 mM  $\text{FeCl}_3$ , 100 mM KCl, 2.5 mM  $\text{K}_3\text{Fe}(\text{CN})_6$ , and 100 mM HCl. To obtain the glucose sensor, 10  $\mu\text{L}$  of the GOx/chitosan/AuNPs mixture was drop-casted onto the PB/AuNFs/Au/PU working area. The mixture contained 30  $\text{mg mL}^{-1}$  GOx, 1 wt% chitosan, and 5  $\text{mg mL}^{-1}$  AuNPs. The modified sensor was allowed to dry at  $4^\circ\text{C}$  for about 24 h. Then, 10  $\mu\text{L}$  of 0.5 wt% Nafion solution was drop-casted on the working electrode. After drying in an ambient atmosphere, the electrode was treated with 2 wt% glutaraldehyde for 30 s. The obtained electrode was thoroughly rinsed with  $10\times$  PBS and stored at  $4^\circ\text{C}$  when not in use.

## 2.4. Preparation of Hydrogel/PU Nanomesh

The hydrogel precursor was prepared by dissolving 4 wt% acrylamide, 0.52 wt% sodium alginate, 0.0025 wt% N, N-methylene bisacrylamide, 0.069 wt% calcium carbonate nanopowder, 0.039 wt% ammonium persulfate, and 0.26 wt% tetramethyl-ethylenediamine in deionized water. Then, PU mesh was immersed into the fully degassed precursor. Thermal curing was conducted at  $60^\circ\text{C}$  for 2.5 h to obtain the hydrogel/PU nanomesh.

## 2.5. Cell Culture Procedure

HSF-T25 cells were grown in Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS, and  $1\times$  penicillin/streptomycin in a sterile  $\text{CO}_2$  incubator at  $37^\circ\text{C}$  and 5 %  $\text{CO}_2$ . When the density of the cells reached 60–70 %, subculture treatment was considered. Cells were transferred into a 12-well plate for 24 h before the experiment. The density was  $8 \times 10^4$  cells per well.

## 2.6. Characterization and Testing

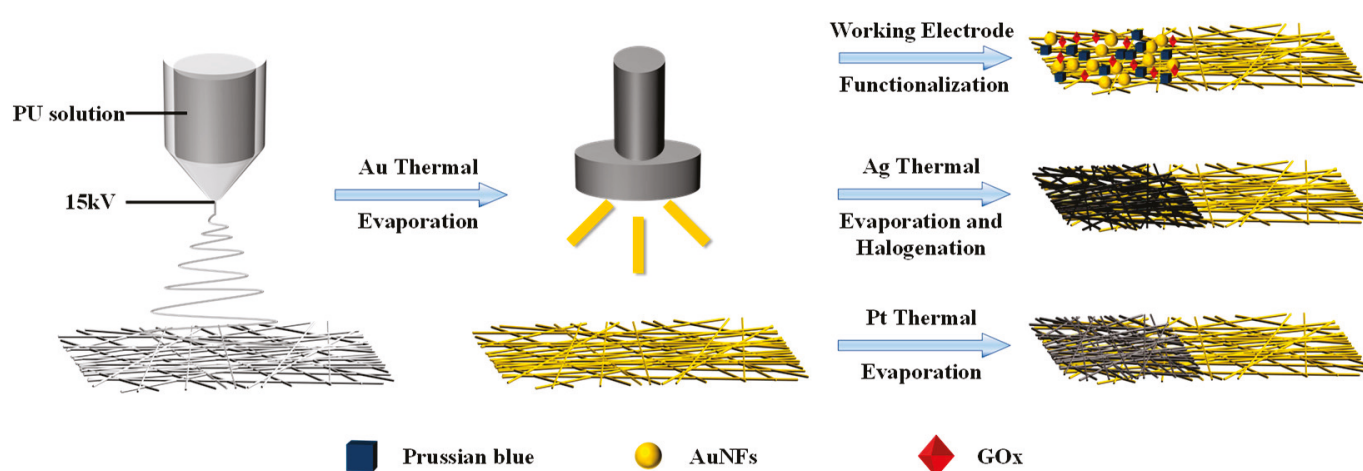
Scanning electron microscope (SEM) and energy-dispersive X-ray spectroscopy (EDS) measurements were performed using JCM-7000 (JEOL, Tokyo, Japan) and GeminiSEM 300 (ZEISS, Oberkochen, Germany). Laser cutting was completed using the 50 W  $\text{CO}_2$  laser cutter Universal VLS2.30DT (Universal Laser System, Arlington Heights, IL, USA). The electrochemical tests, including cyclic voltammetry, chronoamperometry, and EIS, were

implemented using PGSTAT302N (Autolab, Arbon, Switzerland). EIS was conducted at a frequency range of 0.01 Hz–100 kHz by applying a sinusoidal signal with an amplitude of 5 mV in 0.1 M KCl containing 5 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$ . The measured EIS spectra were fitted to an equivalent circuit model (Figure S2, insert). The test configuration was in a 3-probe system with Pt as the counter electrode and Ag/AgCl as the reference electrode. Glucose solutions at varied concentrations were obtained based on  $10\times$  PBS (pH 7.2–7.4). Chronoamperometry was conducted at 0.05 V. The cells were observed using a confocal microplate imaging detection system (BioTek Cytation C10, Agilent, Beijing, China). The sensors were stored at 4 °C in PBS when not in use.

### 3. Result and Discussion

#### *Preparation of Standalone Electrodes*

Figure 1 shows the fabrication method of standalone electrodes based on electrospinning fiber, with the specific fabrication parameters detailed in Materials and Methods.

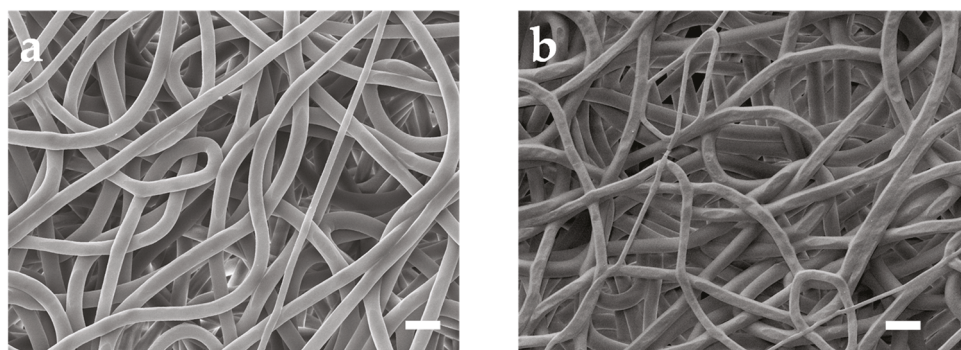


**Figure 1.** Diagram of the mesh fabrication procedure.

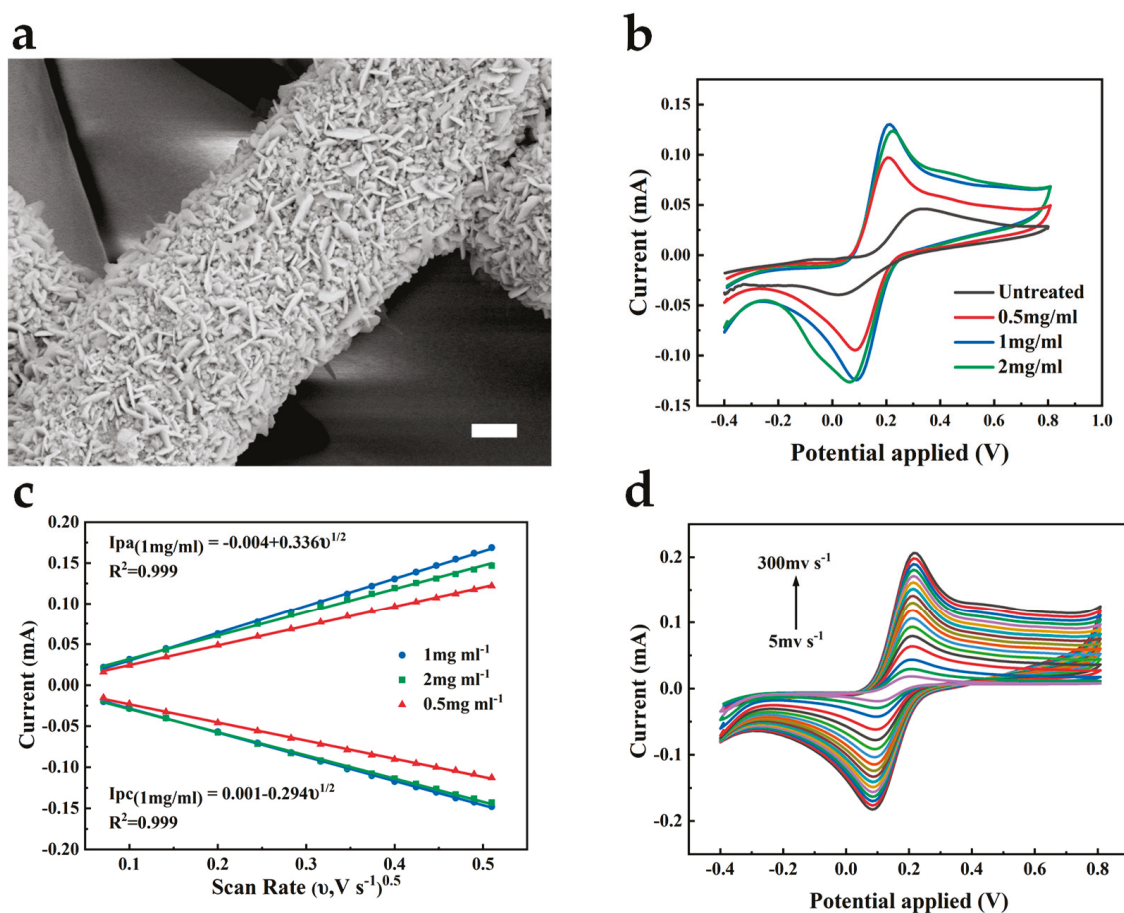
Figure 2a depicts the SEM photo of untreated PU mesh. Due to the electric field formed by the high voltage applied between the needle containing the PU solution and the collector during the electrospinning process, the electrostatic repulsion force overrides the surface tension. Accompanied by the evaporation of the solvent, a mesh structure constructed with randomly oriented PU nanofibers forms on the collector [16]. Then, we removed the mesh from the aluminum foil using a PET frame with a thickness of 125  $\mu\text{m}$ . The obtained PU mesh was placed flat on a silicon wafer with the assistance of PI tape. Then, the wafer with PU mesh was fixed in the evaporation chamber. After that, a 100-nm-thick Au layer was thermally evaporated on the surfaces of the wafer as well as PU mesh at a speed of 1  $\text{\AA}/\text{s}$ . Removing the PI tape allows the silicon wafer and PU mesh to be easily separated without destroying Au-coated fibers. The stacked nanofibers covering Au can form a well-connected conductive network. The different fiber surfaces can be observed in the SEM image of the Au mesh (Figure 2b). In addition, a layer of Pt and Ag was thermally evaporated onto the Au layer to enhance the integrated electrodes' electrochemical stability. The Ag/Au/PU electrode was then treated with  $\text{FeCl}_3$  solution to obtain Ag/AgCl as the reference electrode.

Here, to enhance the electrochemical catalytic ability of the bare gold electrode, we chose to modify the electrode with Au nanomaterials. Due to their large specific surface area, high conductivity, and biocompatibility, their attachment to the electrode benefits the acceleration of the electron transfer rate in the electrode reaction, thus amplifying the response current and related sensitivity [17]. As shown in Figure 3a, Au nanoflakes are uniformly deposited on the Au/PU nanofibers, which further increase the specific surface area of the electrode. To validate the role of AuNFs, we performed cyclic voltammetry measurements on the untreated Au electrode and the electrode after the deposition of

AuNFs using the  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  redox probe, as shown in Figure 3b. We can observe the quasi-reversible behavior of the redox probe on both electrodes. Compared to the bare Au electrode, the AuNFs-treated electrode shows a larger oxidation–reduction current. It reflects the enhanced electrocatalytic ability of the electrode by the electrodeposited AuNFs, thereby improving the electrochemical active surface area of the electrode. The fiber width of the electrode increased with the  $\text{HAuCl}_4$  concentration and reached its most prominent value at a concentration of  $2 \text{ mg mL}^{-1}$  (Figure S1).



**Figure 2.** SEM images of the (a) untreated PU mesh and (b) Au-coated PU mesh. Scale bars, 10  $\mu\text{m}$ .



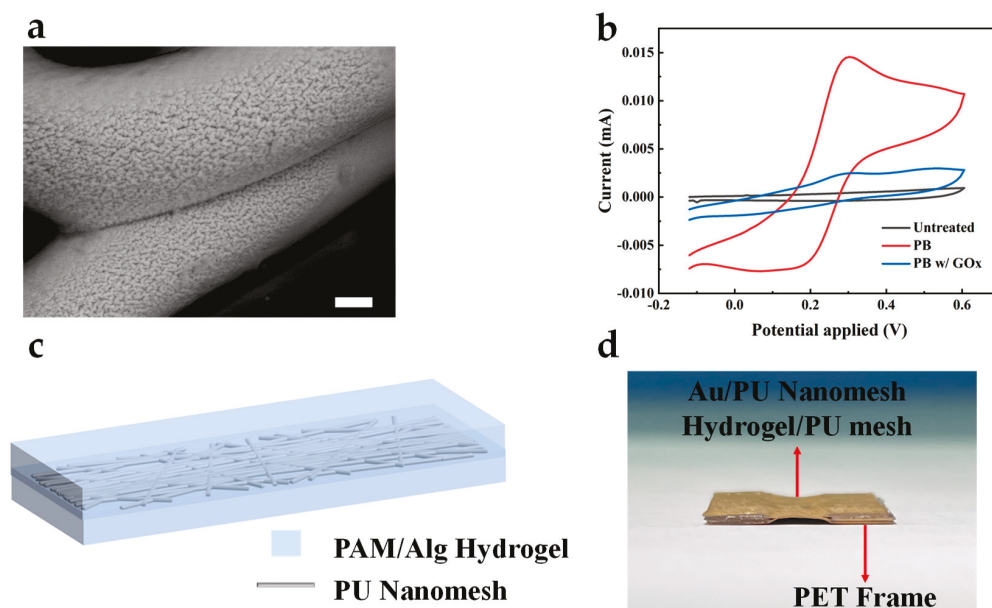
**Figure 3.** (a) SEM image of the AuNFs-deposited Au/PU mesh. Scale bar, 1  $\mu\text{m}$ . (b) CV curves of different treated electrodes in 0.1 M KCl containing 5 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$ . Scan rate  $50 \text{ mV s}^{-1}$ . (c) The calibration plot of the peak current versus the square root of the scan rate of different treated electrodes. (d) CV curves of  $1 \text{ mg mL}^{-1}$  treated electrode at different scan rates in 0.1 M KCl containing 5 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$ .



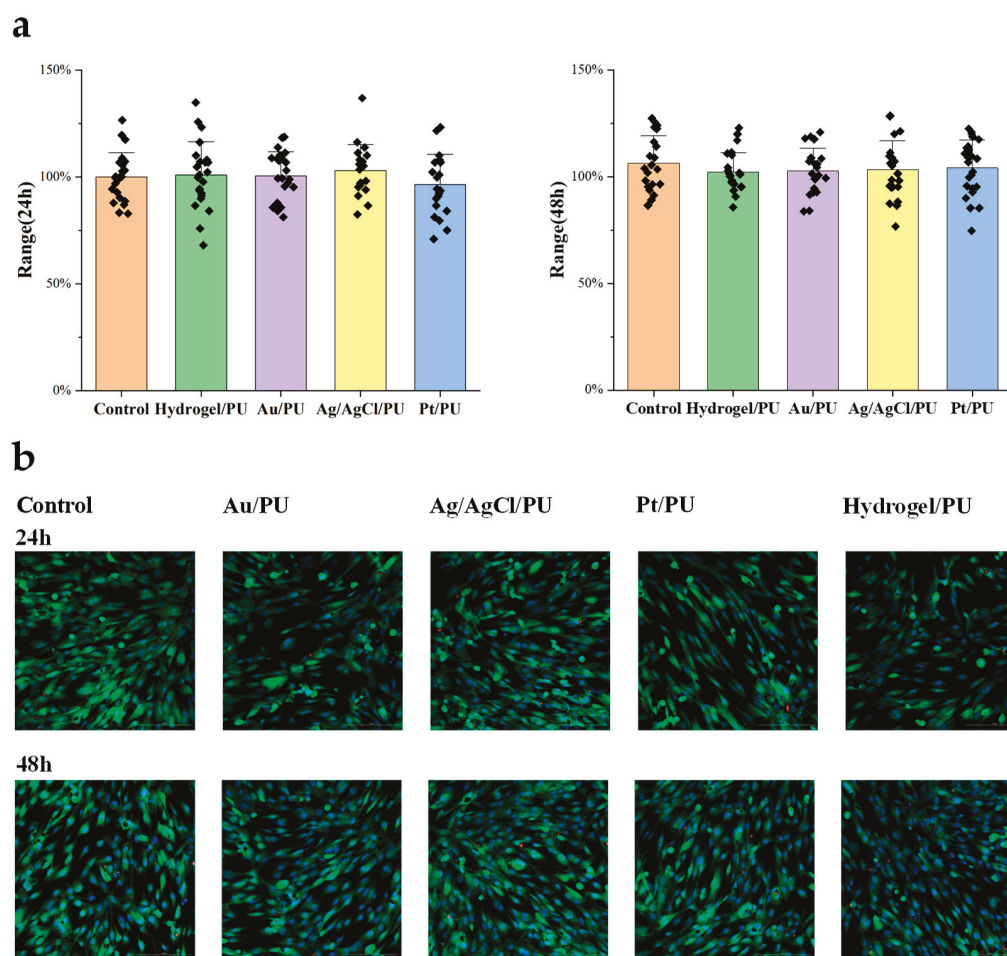
According to the electrochemical surface area, the  $\text{HAuCl}_4$  concentration was studied to optimize the electrodeposited AuNFs. The AuNFs-treated electrode showed the most significant response current and the smallest peak-to-peak separation when the  $\text{HAuCl}_4$  concentration was  $1 \text{ mg mL}^{-1}$  (Figure 3b). We also measured the cyclic voltammograms of the AuNFs/Au/PU electrodes deposited at different  $\text{HAuCl}_4$  concentrations under different scan rates. Compared with other concentrations, the peak current of the electrode pretreated at  $1 \text{ mg mL}^{-1}$  showed a higher slope to the square root of the scan rate, as shown in Figure 3c. According to the Randles–Sevcik equation, the electrode treated at a concentration of  $1 \text{ mg mL}^{-1}$  can exhibit a larger electrochemical active surface area, demonstrating that the oxidation-reduction reaction on the electrode is a diffusion-controlled process. Simultaneously, this electrode can still maintain the shape of the cyclic voltammetry curves at a high scanning speed of  $300 \text{ mV s}^{-1}$ , reflecting the high efficiency of electron transfer on the electrode surface and the excellent conductivity of the electrode, as shown in Figure 3d. According to the EIS spectra of electrodes deposited by different concentrations of  $\text{HAuCl}_4$  (Figure S2), the electrode treated with  $1 \text{ mg mL}^{-1}$  of  $\text{HAuCl}_4$  showed the lowest charge transfer resistance ( $R_{\text{ct}} = 77 \Omega$ ), whereas the  $R_{\text{ct}}$  of the  $2 \text{ mg mL}^{-1}$  treated electrode was  $90 \Omega$  and that of the  $0.5 \text{ mg mL}^{-1}$  treated electrode was  $176 \Omega$ . The result implies that electrodes treated with  $1 \text{ mg mL}^{-1}$   $\text{HAuCl}_4$  are more feasible for electron transfer.

The enzymatic oxidation of glucose mediated by GOx generates hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) as a byproduct. PB is renowned for its electrocatalytic behavior towards  $\text{H}_2\text{O}_2$ , making it suitable for the AuNFs/Au/PU electrode mentioned above. Figure 4a shows the surface morphology of PB deposited on the electrode via cyclic voltammetry. Compared to the uncoated bare electrode, the PB-modified electrode showed a wrinkled surface, indicating the successful electrodeposition of PB. The electrochemical characterization of the GOx/PB/AuNFs/Au/PU electrode, PB/AuNFs/Au/PU electrode, and bare Au electrode in PBS solution was performed using cyclic voltammetry, as shown in Figure 4b. Due to the lack of an electrochemical redox probe on the bare gold electrode, no evident redox current peak is observed in its cyclic voltammetry curve. However, upon the electrode's coating with PB, the reversible electrochemical behavior of PB on the electrode is observed in the PBS solution, indicating the successful deposition of PB on the electrode. To assemble the standalone electrospun electrodes into an all-fiber three-electrode system, we introduced a double-network hydrogel based on polyacrylamide-sodium alginate as an adhesive and substance-transferring layer for the independent electrodes. An electrospun mesh was incorporated into the hydrogel system to enhance its mechanical strength. Figure 4c shows the schematic of the electrospun mesh-reinforced hydrogel, and the preparation method is presented in Materials and Methods. To evaluate the adhesion performance of the hydrogel, Au/PU electrodes carried by laser-cut PET were assembled into a five-layer structure (A/H/A/H/A) using the prepared hydrogel and placed in deionized water. After 2 weeks, the structure maintained stable adhesion and good conductivity, as shown in Figure 4d. This demonstrates that the hydrogel could be applied to long-term monitoring while retaining good adhesion.

To evaluate the biocompatibility of the all-fiber sensor, we designed an experiment to study the cytotoxicity of the meshes assembled into the sensor. The Materials and Methods section shows the specific cell culture and passage steps. First, we cultured human skin fibroblasts in a 12-well plate until they covered the bottom of the dish. Then, we added approximately  $5 \text{ mm}^2$  of the mesh to be tested to the culture dish. After 24 h and 48 h, we took images and counted the cells. After co-culturing with the mesh for 48 h, we did not observe significant differences in cell morphology and cell proliferation activity compared to the control group. Therefore, the cytotoxicity results indicate that the resultant meshes have good biocompatibility and meet the requirements for further implantable monitoring (Figure 5).



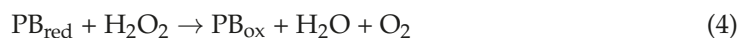
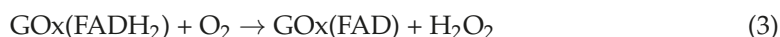
**Figure 4.** (a) SEM image of the PB-deposited AuNFs/Au/PU mesh. Scale bar, 1  $\mu\text{m}$ . (b) CV curves of GOx/PB/AuNFs/Au/PU, PB/AuNFs/Au/PU, and AuNFs/Au/PU electrode in  $10\times$  PBS. (c) Schematic of electrospun mesh-reinforced hydrogel. (d) The optical images of the five-layer structure after 2 weeks immersed in deionized water.



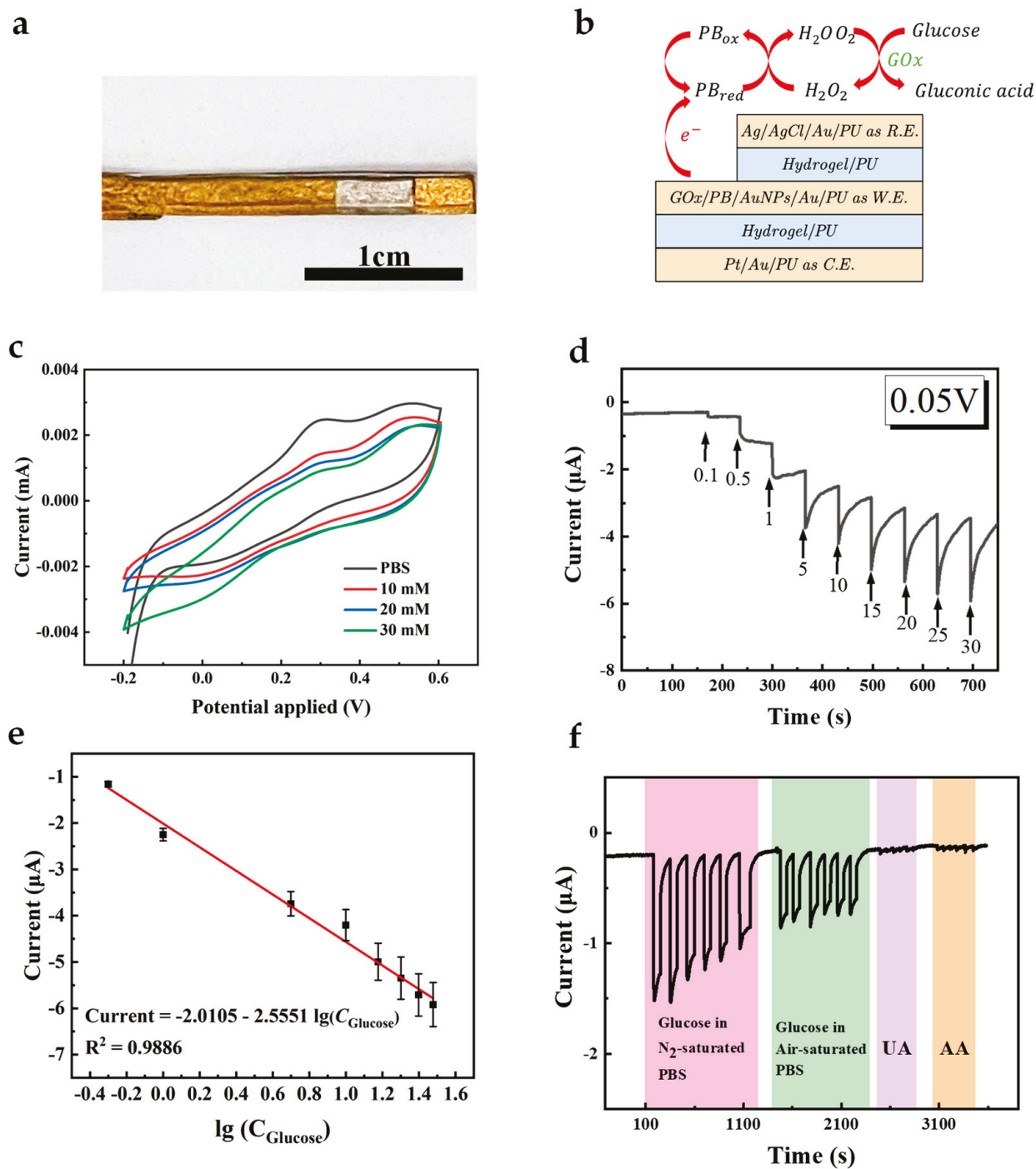
**Figure 5.** (a) Cell numbers after 24 h (left) and 48 h (right) treatment. (b) Representative fluorescence images of different treated cells.



The successful modification of AuNFs, PB, and GOx on the working electrode was demonstrated. To enhance the electron exchange rate between the active sites of GOx and the working electrode, GOx was mixed with water-dispersed AuNPs to modify the working electrode. Figure 6a,b show the conceptual schematic and pictures of the all-fiber electrode assembled using the hydrogel-PU mesh, with the independent electrodes acting as working electrode, counter electrode, and reference electrode, forming a whole sensor system. The sensing principle based on PB and GOx is illustrated in Equations (1)–(5). In the absence of oxygen (Equations (1), (2) and (5)), i.e., in an N<sub>2</sub>-saturated environment, glucose is first catalyzed by GOx to gluconic acid, with the flavin adenine dinucleotide (FAD) cofactor in GOx being converted to the reduced cofactor flavin adenine dinucleotide (FADH<sub>2</sub>). PB, acting as the mediator, reacts with FADH<sub>2</sub> to form PB in its reduced form (PB<sub>red</sub>). Subsequently, PB<sub>red</sub> can be oxidized at the electrode surface, allowing continuous cycling of the mediator and enabling the glucose oxidation process to proceed. In the presence of oxygen (Equations (1) and (3)–(5)), the reaction in Equation (1) occurs similarly, followed by oxygen accepting electrons from FADH<sub>2</sub>, producing H<sub>2</sub>O<sub>2</sub> and FAD. In the presence of PB, H<sub>2</sub>O<sub>2</sub> is reduced, and PB in its oxidized form (PB<sub>ox</sub>) is generated. Subsequently, PB<sub>ox</sub> is reduced to PB<sub>red</sub> at the electrode (Figures 6f and S3). CV curves of the resultant electrode in PBS containing different concentrations of glucose were recorded (Figure 6c). As can be seen, CV curves in a glucose-containing solution show a higher reduction current and lower oxidation current, demonstrating that the GOx on the working electrode catalyzes glucose.



To further evaluate the performance of the constructed biosensor, chronoamperometry was employed to measure the analytical performance (Figure 6d). Figure 6e shows the linear relationship between the current response and the logarithmic value of glucose concentration, and the electrode exhibits a distinguishable response in glucose concentration. Good linearity with an R<sup>2</sup> of 0.9886 and sensitivity of 31.94 μA (lg(mM))<sup>−1</sup> cm<sup>−2</sup> were observed at concentrations ranging from 0 to 30 mM, and the detection limit (LOD) calculated at S/N = 3 was 1 mM. This range includes the average glucose concentration of human ISF and diabetes patients [18]. Meanwhile, the current response of the electrode to glucose and other interfering substances (UA, AA) was measured at the same voltage (0.05 V), as shown in Figure 6f. It can be observed that this electrode exhibits high selectivity towards glucose due to the presence of GOx and PB, and its response to interfering substances can be ignored. We conducted continuous tests on the electrode's current response to glucose over 30 days to evaluate the sensor's long-term performance. Minimal current changes were obtained post-30 days, demonstrating the sensor's good long-term stability (Figure S4). When bending is applied to the whole sensor, it can still conduct signals well (Figure S6). It can detect glucose under different bending conditions. To compare our results with others, we have listed a few publications with electrodes for glucose sensing in Table 1. In summary, the as-prepared all-fiber glucose sensor can be well applied in further wearable and implantable monitoring.



**Figure 6.** (a) The optical images of the composite electrode. Scale bar, 1 cm. (b) The diagram of the sensor. (c) CV curve of the  $GOx/PB/AuNFs/Au/PU$  electrode in PBS with and without 10 mM glucose at a scan rate of  $50 \text{ mV s}^{-1}$ . (d) Amperometric response of the  $GOx/PB/AuNFs/Au/PU$  electrode in glucose solutions with different concentrations ranged from 0 mM to 30 mM. (e) The calibration plot of the response current on  $GOx/PB/AuNFs/PU$  electrode ( $n = 3$ ). (f) Amperometric response of the  $GOx/PB/AuNFs/PU$  towards 5 mM glucose in air/ $N_2$ -saturated PBS and 5 mM UA, 0.1 mM AA in  $N_2$ -saturated PBS.

**Table 1.** Comparison of different glucose electrodes.

| Reference | Electrode and Materials                 | Sensitivity                                                    | LOD                | Concentration Range |
|-----------|-----------------------------------------|----------------------------------------------------------------|--------------------|---------------------|
| This work | Electrospun electrode w/ AuNFs/PB       | $31.94 \mu\text{A} (\text{lg}(\text{mM}))^{-1} \text{cm}^{-2}$ | 1.01 mM            | 1–30 mM             |
| [19]      | Solid MN w/ Au/pTCA/GOx                 | $0.22 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$             | 19.4 $\mu\text{M}$ | 0.05–20 mM          |
| [20]      | Electrospun electrode w/ PEDOT/GOx      | $74.22 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$            | 2.9 $\mu\text{M}$  | 0–4.5 mM            |
| [21]      | Graphene/CNT fiber w/GOx                | $14.45 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$            | 0.06 $\mu\text{M}$ | 0–30 mM             |
| [22]      | Electrospun fiber w/ PEDOS: PSS         | $0.386 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$            | 3.31 mM            | 0–30 mM             |
| [23]      | MN array w/ Au/Fc-PAMAM/GOx             | $0.1622 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$           | 660 $\mu\text{M}$  | 1–9 mM              |
| [24]      | Screen printing electrode w/ PPG/GOx/PU | $12.69 \mu\text{A} (\text{mM})^{-1} \text{cm}^{-2}$            | No mention         | 1–30 mM             |

Notes: MN, microneedle; pTCA, polyterthiophene carboxylic acid; PEDOT, poly(3,4-ethylenedioxythiophene); CNT, carbon nanotube; Fc-PAMAM, ferrocene-cored poly(amidoamine); PPG, poly (N-phenylglycine).

#### 4. Conclusions

In this work, we designed and fabricated an all-fiber electrochemical electrode based on electrospinning. A Au conductive network was formed on PU fiber by thermal evaporation. Subsequently, electrochemical deposition was employed to form AuNFs and wrinkled PB on the electrode surface to improve the electrode's electrochemical performance. Then, GOx-AuNPs-chitosan was immobilized on the electrode to detect glucose. A linear response was obtained within the concentration range of 1–30 mM, with a sensitivity of  $31.94 \mu\text{A} (\text{lg}(\text{mM}))^{-1} \text{cm}^{-2}$  and LOD of 1 mM ( $S/N = 3$ ). The sensor also exhibited good anti-interference performance against UA and AA. Therefore, the proposed flexible sensor is a reliable device for health monitoring, providing new insights for fiber-based electrochemical sensors. Modification with different functional materials can achieve monitoring of different substances, and it is expected to achieve multimodal sensing.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/s24144580/s1>, Figure S1: The fiber widths of the electrodes after electrodeposition at different  $\text{HAuCl}_4$  concentrations. Figure S2: The fiber widths of the electrodes after electrodeposition at different  $\text{HAuCl}_4$  concentrations. Figure S3: Changes in sensor current response under different test conditions. Figure S4: The electrode's current response curve to glucose in the 30-day range. Figure S5: Mechanical stability of electrodes. Figure S6: CV curves of the electrode under different bending conditions in the solution with 30 mM glucose.

**Author Contributions:** Conceptualization, T.R., Y.Y., J.J. and J.G.; methodology, Z.T., J.J. and S.L.; validation, Z.T., M.G., Y.L. and S.L.; formal analysis, Z.T. and J.J.; investigation, Z.T. and J.J.; resources, T.R. and Y.Y.; data curation, Z.T., J.J. and S.L.; writing—original draft preparation, Z.T. and J.J.; writing—review and editing, S.J., H.L., T.S. and J.G.; visualization, Z.T., J.J. and S.L.; supervision, T.R.; project administration, J.J., J.G., Y.Y. and T.R.; funding acquisition, T.R., Z.T. and J.J. are co-first authors. All authors have read and agreed to the published version of the manuscript.

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## Article

# Integration of Hollow Microneedle Arrays with Jellyfish-Shaped Electrochemical Sensor for the Detection of Biomarkers in Interstitial Fluid

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**Abstract:** This study integrates hollow microneedle arrays (HMNA) with a novel jellyfish-shaped electrochemical sensor for the detection of key biomarkers, including uric acid (UA), glucose, and pH, in artificial interstitial fluid. The jellyfish-shaped sensor displayed linear responses in detecting UA and glucose via differential pulse voltammetry (DPV) and chronoamperometry, respectively. Notably, the open circuit potential (OCP) of the system showed a linear variation with pH changes, validating its pH-sensing capability. The sensor system demonstrates exceptional electrochemical responsiveness within the physiological concentration ranges of these biomarkers in simulated epidermis sensing applications. The detection linear ranges of UA, glucose, and pH were 0~0.8 mM, 0~7 mM, and 4.0~8.0, respectively. These findings highlight the potential of the HMNA-integrated jellyfish-shaped sensors in real-world epidermal applications for comprehensive disease diagnosis and health monitoring.

**Keywords:** uric acid; glucose; pH; microneedle array; interstitial fluid

## 1. Introduction

With the rapid advancements in biomedical fields and the increasing individual focus on personal health status, the detection of biomarkers within the human body plays a pivotal role in disease diagnosis, prevention, and treatment. Uric acid (UA), for instance, serves as a biomarker for hyperuricemia and gout [1,2]; glucose is an indicator of diabetes or hypoglycemia [3–5]; pH levels are reflective of metabolic health [6] and acid-base balance [7]. Furthermore, elevated serum UA concentrations are regarded as one of the best independent predictors of diabetes, often preceding the development of insulin resistance and type 2 diabetes [8]. There are also reports of an increased prevalence of nephrolithiasis in diabetic patients, with low urinary pH being the principal factor in uric acid stone formation [9]. Consequently, glucose, uric acid, and pH, as biomarkers, are interconnected in disease diagnostics. Moreover, the pH of the medium can influence the detection of other biomarkers, such as uric acid and glucose, by affecting the acidity or alkalinity of solutions or the activity of enzymes [10]. Therefore, the concurrent measurement of glucose, uric acid, and pH is of substantial importance for comprehensive diagnostics of related diseases.

Clinically, the most prevalent biofluid sampled for health or disease monitoring-related biomarkers is blood. However, invasive blood collection typically necessitates trained medical personnel, exposes the subject to infection risks, and imposes considerable



psychological stress. Alternatively, non-invasive or minimally invasive biomarker sampling offers a new avenue for health monitoring and disease diagnosis, facilitating convenient and rapid testing for related conditions [11]. This approach can empower personalized medicine, precision therapy, and individual self-health management. Extensive research has explored non-invasive or minimally invasive methods to sense biomarkers in a variety of bodily fluids, including sweat [12], tears [13], saliva [14], urine [15], and interstitial fluid (ISF) [16]. Yet, more accessible bodily fluids (e.g., sweat, tears, saliva, and urine) suffer from inconsistency in sample collection, dilution, compositional variations, and heightened susceptibility to contamination.

ISF, formed by plasma extravasation from capillaries, serves as the medium for exchanging signaling molecules, nutrients, and waste between capillaries and surrounding tissues and cells. Compared to blood, ISF resides closer to the skin surface and can be harvested painlessly or with minimal discomfort using minimally invasive techniques, without clotting or blood cell interference. ISF harbors valuable biomarkers relevant to health monitoring and disease diagnosis, such as glucose, UA, urea, lactate, cortisol,  $\text{Na}^+$ ,  $\text{K}^+$ , and so on, whose concentrations mirror those in blood [17,18]. To a certain extent, ISF is thus seen as an alternative biofluid to blood for diagnostic purposes [19].

The extraction of ISF via microneedles for minimally invasive sampling is currently one of the popular methodologies in studying biomarkers sensing within ISF [20–23]. Typically, these microneedles, ranging in length from 500 to 1000  $\mu\text{m}$ , painlessly penetrate the human stratum corneum barrier to facilitate biomarker retrieval from ISF. Over the past decades, microneedle technology has rapidly progressed from single biomarker detection to the analysis of multiple biomarkers, allowing for a more comprehensive assessment of an individual's health status [24–27]. Conventional biomarker assays, such as the enzyme-linked immunosorbent assay (ELISA), are time-consuming, labor-intensive, and require specialized equipment or skilled operators, making them less amenable to adoption as portable personal health monitoring tools. Recently, there has been a report of the simultaneous colorimetric detection of glucose, uric acid, and pH [28]. Electrochemical sensing methods for biomarkers, on the other hand, allow for the easy miniaturization of devices and offer rapid, sensitive detection, thereby presenting a quick and convenient means for individual biomarker analysis.

This study employs 3D printing to construct a polymer hollow microneedle array (HMNA) and combines paper-cutting with printing techniques for electrode fabrication, thereby fabricating a jellyfish-shaped multifunctional electrochemical sensor. By integrating the HMNA with the electrochemical sensor, we pioneer its use for the electrochemical sensing of three biomarkers—uric acid, glucose, and pH—in interstitial fluid. This approach provides more holistic information for disease diagnosis and health management.

## 2. Experimental

### 2.1. Chemicals and Materials

The following reagents were acquired from specified suppliers:  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  ( $\geq 99\%$ ),  $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$  ( $\geq 99\%$ ),  $\text{NaCl}$  ( $\geq 99.8\%$ ),  $\text{CaCl}_2$  ( $\geq 96\%$ ), D(+)-glucose anhydrous ( $\geq 99.5\%$ ), sucrose ( $> 99\%$ ), agarose,  $\text{KCl}$  ( $\geq 99.5\%$ ),  $\text{FeCl}_3$  ( $\geq 97\%$ ),  $\text{HCl}$  (36%~38%),  $\text{K}_3\text{Fe}(\text{CN})_6$  ( $\geq 99.5\%$ ), ascorbic acid ( $\geq 99.7\%$ ), ethanol,  $\text{H}_2\text{O}_2$  (30%), acetic acid ( $\geq 99.8\%$ ), lactic acid (85–92%),  $\text{NaOH}$  ( $\geq 96\%$ ),  $\text{MgSO}_4$  ( $\geq 98\%$ ), and HEPES ( $\geq 99\%$ ) were all sourced from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Britton-Robinson buffer was purchased from Shanghai Yuanye Bio-Technology Co., Ltd. (Shanghai, China). Glucose oxidase (GOD,  $\geq 100$  U/mg) was supplied by Sangon Biotech (Shanghai, China). Uric acid ( $\geq 98\%$ ) was obtained from TCI Shanghai. The photopolymer resin was provided by Shenzhen Anycubic Technology Co., Ltd. (Shenzhen, China). Nafion (5 wt%) and chitosan (medium molecular weight) were both purchased from Sigma-Aldrich (Shanghai, China). -COOH Functionalized Multi-walled Carbon Nanotubes (MWCNT-COOH,  $\geq 98$  wt%) were sourced from Chengdu Organic Chemicals Co. Ltd. (Chengdu, China). The carbon and silver/silver chloride (60:40) inks were bought from SunChemical Co. (Parsippany, NJ,

USA). A 0.1 M phosphate buffer solution (PBS) with a pH of 7.4 was prepared using  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  and  $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ . All chemical substances were employed without undergoing any additional purification steps. Throughout the experiments, deionized water of high purity, generated by a Milli-Q system ( $18.2 \text{ M}\Omega \cdot \text{cm}$  at  $25^\circ\text{C}$ ), was utilized.

## 2.2. Apparatus

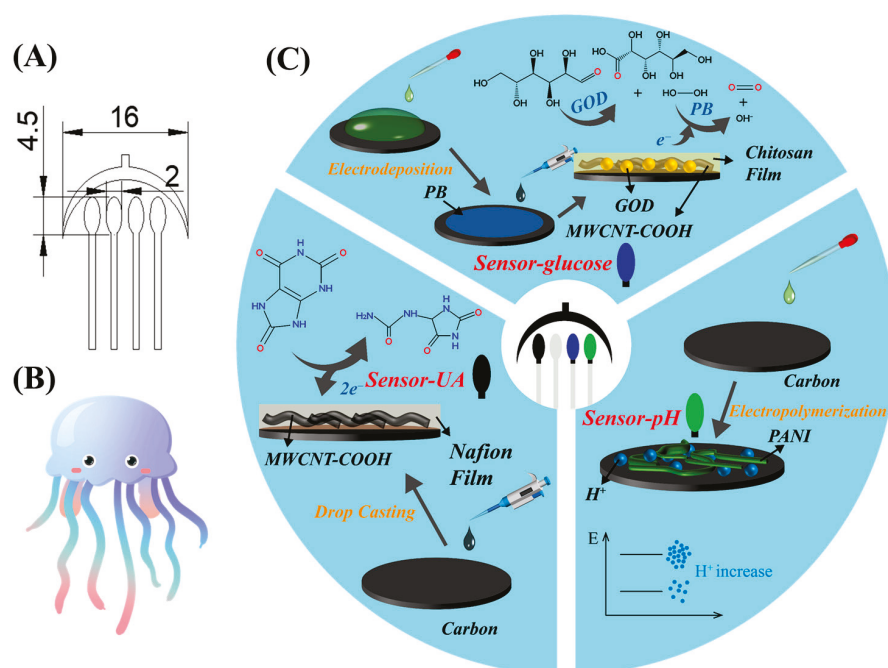
Electrochemical evaluations were performed using a CHI-760e workstation (Austin, TX, USA). Electrode printing stencils were cut on vinyl transfer film using a Roland desktop cutter GS-24. The fabrication of hollow microneedle arrays was carried out using a PHOTON MONO X 6K 3D printer (Shenzhen Anycubic Technology Co., Ltd., Shenzhen, China). Morphological observations were conducted utilizing a ZEISS Gemini 300 scanning electron microscope (SEM, Oberkochen, Germany).

## 2.3. Preparation of Artificial Interstitial Fluid (AIF)

The artificial interstitial fluid was prepared by mixing 2.5 mM  $\text{CaCl}_2$ , 5.5 mM glucose, 10 mM HEPES, 3.5 mM KCl, 0.7 mM  $\text{MgSO}_4$ , 123 mM NaCl, 1.5 mM  $\text{NaH}_2\text{PO}_4$ , and 7.4 mM sucrose solution, with the final pH of the solution adjusted to 7.0 [29].

## 2.4. Preparation of the Electrodes

A jellyfish-shaped electrode printing stencil was designed using CAD software (AutoCAD 2021), with the electrode design and dimensions depicted in Figure 1A. Figure 1B illustrates the electrode's resemblance to a jellyfish-shape. The corresponding electrode stencils were then cut onto a vinyl transfer film using Roland desktop cutter. Subsequently, the stencil was affixed onto a PET board, upon which the electrodes were sequentially printed using appropriate inks. The wire section connecting to the electrochemical workstation is composed of 1.3 mm wide Ag/AgCl, while the reference electrode is also made of Ag/AgCl. Both the working and counter electrodes are carbon-based. The geometric area of each working electrode, as well as that of the reference electrode, was  $7.065 \text{ mm}^2$ . After applying each type of ink, the PET board was placed in a  $60^\circ\text{C}$  oven for a 20-min drying period.



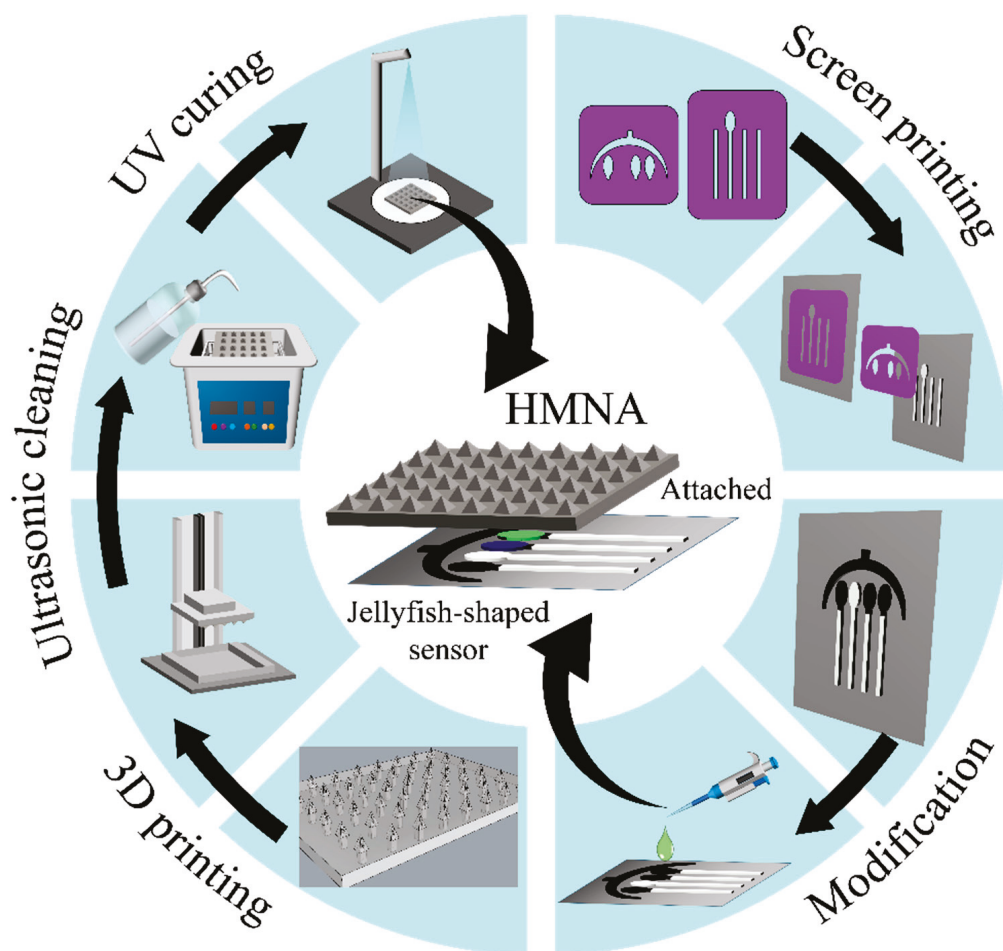
**Figure 1.** (A) Electrode design and dimensions (unit: mm), (B) which resembles a jellyfish, and (C) the distribution and modification of the electrodes of the jellyfish-shaped sensor, as well as the electrochemical sensing principles of each electrode.

The distribution and modification of the electrodes of the jellyfish-shaped sensor, as well as the electrochemical sensing principles of each electrode, are illustrated as shown in Figure 1C.

## 2.5. Preparation of Hollow Microneedle Array (HMNA)

The HMNA was modeled using RHINO 8 3D software (Version 8.2), followed by 3D printing using a PHOTON MONO X 6K 3D printer (<https://store.anycubic.com/products/photon-mono-x-6k>, accessed on 25 April 2024). The array comprised  $6 \times 8$  microneedles, each with a pyramidal shape, a height of  $800\ \mu\text{m}$  and a hollow microchannel diameter of  $100\ \mu\text{m}$ . Upon completion of printing, the HMNA underwent demolding treatment and was immersed in ethanol (95%) for ultrasonic cleaning for 3 min to remove uncured resin. Finally, the HMNA was subjected to ultraviolet cleaning in a UV cleaner for 10 min to finalize the shape.

The electrode printing, HMNA 3D printing, and their coupled testing configuration are illustrated in Figure 2. In the test, the sensors were in direct contact with the back side of HMNA, where the HMNA served to extract ISF while the sensors promptly detected the biomarkers from the ISF sampled by the HMNA.



**Figure 2.** The schematic diagram of the electrode printing, HMNA 3D printing, and their coupled testing configuration.

## 2.6. Preparation of the Sensor

### 2.6.1. Preparation of Sensor-UA

The preparation method for the Sensor-UA is similar to our previous work [24]. Specifically, a 5 wt% Nafion solution was first diluted with deionized water to obtain a

2 wt% Nafion solution. Subsequently, 1 mg of MWCNT-COOH was mixed with 1 mL of the 2 wt% Nafion solution under ultrasonic assistance for half an hour. Finally, 4  $\mu$ L of the MWCNT-COOH/Nafion mixture was drop-cast onto a carbon working electrode. After natural air-drying, the resulting sensor was designated Sensor-UA.

#### 2.6.2. Preparation of Sensor-Glucose

First, Prussian Blue (PB) was electrodeposited onto an unmodified carbon working electrode. The procedure involved adding a mixture of 2.5 mM FeCl<sub>3</sub>, 2.5 mM K<sub>3</sub>[Fe(CN)<sub>6</sub>], 100 mM KCl, and 100 mM HCl onto the electrode surface, followed by performing 10 cyclic voltammetry (CV) cycles at a scan rate of 50 mV/s within the potential range of  $-0.2$  V to  $0.6$  V, thus depositing PB. After rinsing the modified electrode with deionized water, it was placed in an oven at  $90$  °C for 4 h. Figure S1A presents the cyclic voltammogram of PB deposition.

Subsequently, GOD was immobilized onto the PB-modified electrode. This was accomplished by dispersing 2 mg MWCNT-COOH in 1 mL of a mixture containing 1 wt% acetic acid and 2 wt% chitosan, followed by mechanically stirring overnight to yield an MWCNT-COOH/chitosan mixture. Then, GOD was dissolved in PBS to prepare a 40 mg/mL GOD solution. The GOD solution was then mixed with the MWCNT-COOH/chitosan mixture at a volume ratio of 1:2, forming a GOD/MWCNT-COOH/chitosan composite. Finally, 4  $\mu$ L of the GOD/MWCNT-COOH/chitosan composite was drop-cast onto the PB-modified electrode, which was then incubated overnight in a refrigerator at  $4$  °C. The prepared sensor was designated Sensor-glucose.

#### 2.6.3. Preparation of Sensor-pH

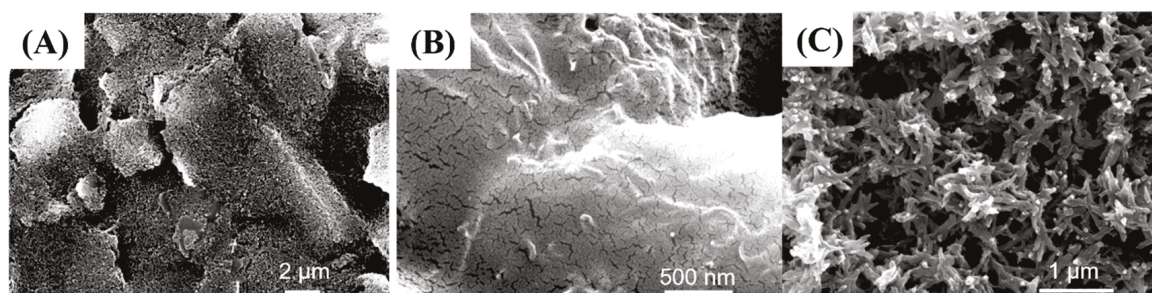
First, 0.5 M HCl was drop-cast onto the surface of an unmodified carbon electrode. Subsequently, 10 CV cycles were performed within the potential range of  $-0.1$  V to  $0.9$  V at a scan rate of  $0.1$  V/s to electrochemically clean the electrode. After rinsing the electrode with deionized water, a mixture containing 0.1 M aniline and 1 M HCl was added onto the electrode surface. Under the potential range of  $-0.2$  V to  $1.0$  V and a scan rate of  $0.1$  V/s, 12 CV cycles were conducted on the electrode to facilitate the electropolymerization of polyaniline. The modified electrode was then rinsed again with deionized water and designated Sensor-pH. Figure S1B displays the CV curves of aniline electropolymerization.

### 3. Results and Discussion

#### 3.1. SEM Characterization

To observe the surface morphology of each modified electrode of the sensor, we characterized the electrodes using SEM. As shown in Figure 3A, the unmodified carbon electrode exhibited a stacked lamellae structure. The surface of the lamellar was rough, formed by numerous closely packed carbon particles, ensuring the electrical conductivity of the substrate electrode for the sensor. Figure 3B presents the SEM image of the MWCNT-COOH/Nafion-mixture-modified electrode, clearly revealing a distinct Nafion film covering the electrode surface. The Nafion film served to prevent the detachment of MWCNT-COOH from the electrode. Despite the MWCNT-COOH being effectively encapsulated by the Nafion membrane, the modified electrode surface still retained the characteristic fibrous structure of MWCNT-COOH. Figure 3C displays the surface structure of the electropolymerized polyaniline. It demonstrates that the electrode surface is composed of fibrous polyaniline, the typical feature of the morphology of electropolymerized polyaniline [30].





**Figure 3.** The SEM characterization of the modified electrodes: (A) unmodified carbon electrode, (B) MWCNT-COOH/Nafion-mixture-modified electrode, and (C) electropolymerized polyaniline modified electrode.

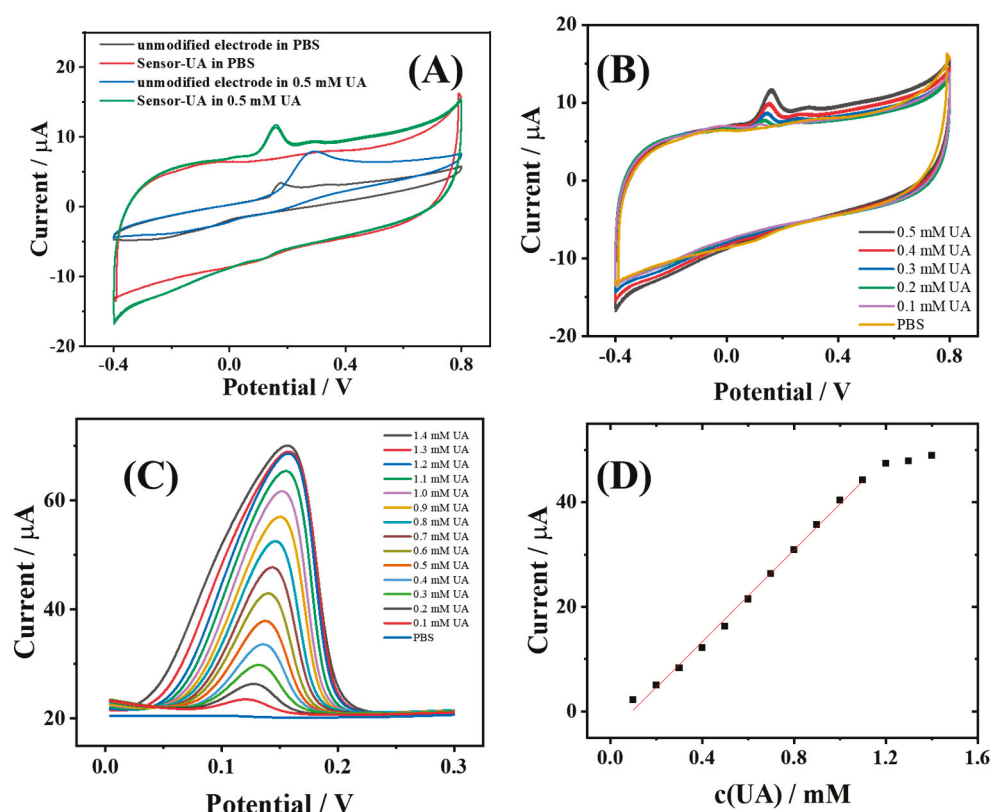
### 3.2. Electrochemical Performance of the Jellyfish-Shaped Sensor

#### 3.2.1. Sensor-UA

To characterize the electrochemical performance of Sensor-UA, the CV behaviors of UA on the electrode before and after modification with MWCNT-COOH were initially examined; the results are depicted in Figure 4A. It can be observed that an oxidative peak at approximately 0.17 V for the unmodified MWCNT-COOH electrode in PBS is likely due to the electrochemical oxidation of inherent impurities present in the commercial carbon ink. Upon the addition of 0.5 mM UA, an oxidative peak corresponding to UA appeared at 0.29 V for the unmodified carbon electrode, which should be attributed to the electrochemical oxidation of UA, involving the transfer of two electrons on the electrode surface, leading to the formation of allantoin. For comparison, the electrochemical CV behavior of the MWCNT-COOH-modified carbon electrode (Sensor-UA) in PBS was then investigated. As is evident from the figure, the electric double layer of the Sensor-UA broadened relative to that of the unmodified carbon electrode. This should be due to the increase in the electrode surface area resulting from the MWCNT-COOH modification. Moreover, the oxidative peak associated with impurities that was observed at around 0.17 V for the unmodified electrode disappeared. This is presumably because the substantial increase in electrode surface area caused by the introduction of MWCNT-COOH generating an augmented electric double-layer current that masked the electrochemical oxidation peak of impurities present in the unmodified carbon electrode. Subsequently, Sensor-UA was spiked with 0.5 mM UA in the solution, and an oxidative peak at 0.16 V was revealed. This can also be assigned to the electrochemical oxidation of UA. Notably, the oxidative peak potential of UA on Sensor-UA was lower than that on the unmodified carbon electrode, indicating that the modification with MWCNT-COOH enabled Sensor-UA to effectively reduce the electrochemical oxidation potential of UA, thereby exhibiting a superior UA electrochemical oxidation performance.

To further explore the sensing potential of Sensor-UA towards UA, we tested its CV-response characteristics upon the addition of different concentrations of UA, as illustrated in Figure 4B. It is evident that as the concentration of UA was increased stepwise from 0 to 0.5 mM, the oxidative peak current of Sensor-UA, corresponding to UA, also increased, accompanied by a progressive shift in the peak potential towards more positive values. The gradual positive shift in the electrochemical oxidation peak with increasing UA concentration may result from a combination of mass transport effects, changes in electrode surface coverage, and the electrode local environment. These observations substantiate the electrochemical sensing capability of Sensor-UA for UA.





**Figure 4.** The electrochemical characterization of Sensor-UA: (A) CVs of unmodified and MWCNT-COOH-modified carbon electrodes in 0.1M PBS, pH 7.4, in the absence and presence of 0.5 mM UA. Potential range  $-0.4$  V to  $0.8$  V; scan rate  $50$  mV/s. (B) CVs of Sensor-UA with different concentrations of UA in PBS. UA concentrations were  $0$ ,  $0.1$ ,  $0.2$ ,  $0.3$ ,  $0.4$ , and  $0.5$  mM, respectively. Potential range  $-0.4$  V to  $0.8$  V; scan rate  $50$  mV/s. (C) DPV responses of Sensor-UA to different concentrations of UA from  $0.1$  to  $1.4$  mM. Potential range  $0$  V to  $0.3$  V; amplitude  $0.05$  V; pulse width  $0.05$  s. (D) The linear fitting curve of calibration for Sensor-UA's DPV current response towards UA.

Differential pulse voltammetry (DPV) can be utilized effectively to subtract background currents from the sensor, enabling the acquisition of pronounced current response information corresponding to target species concentrations. To assess the electrochemical sensing performance of Sensor-UA towards UA, DPV was employed to investigate the sensor's response to varying UA concentrations, as shown in Figure 4C. With the UA concentration incrementally increasing from  $0$  to  $1.4$  mM, the DPV response peak current of Sensor-UA for UA steadily rose. The calibration curve depicting this response is presented in Figure 4D. It can be deduced that Sensor-UA exhibited a linear response range for UA spanning from  $0.1$  to  $1.2$  mM, with a sensitivity of  $43.81 \mu\text{A}/\text{mM}$  and a detection limit of  $0.01 \mu\text{M}$  ( $S/N = 3$ ). The linear fitting equation for this calibration curve is as follows:

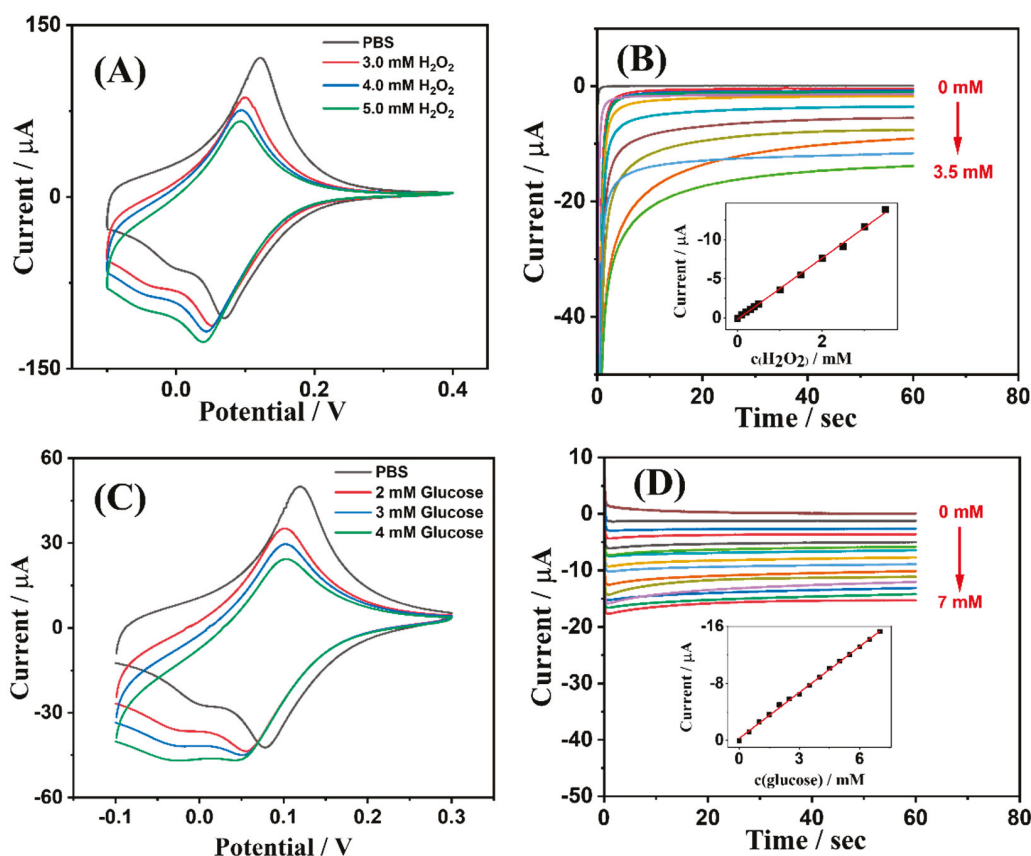
$$I (\mu\text{A}) = 43.81 \times c(\text{UA}) (\text{mM}) - 4.18 (\mu\text{A}) \quad (R^2 = 0.9956)$$

The results of the reusability and anti-interference performance tests for Sensor-UA are depicted in Figure S2, showcasing its excellent reusability and robust anti-interference capabilities.

### 3.2.2. Sensor-Glucose

In the electrochemical sensing process of Sensor-Glucose for glucose, glucose is first enzymatically oxidized by GOD in the presence of oxygen, producing gluconic acid and  $\text{H}_2\text{O}_2$ . The generated  $\text{H}_2\text{O}_2$  is subsequently electrochemically reduced at the PB-modified electrode. The magnitude of this current is directly proportional to the glucose concen-

tration [31]. Thus, to investigate the glucose electrochemical sensing performance of Sensor-Glucose, the  $\text{H}_2\text{O}_2$  electrochemical sensing performance of the PB-modified electrode was first examined. As shown in Figure 5A, it presents cyclic voltammograms of the PB-modified electrode for various concentrations of  $\text{H}_2\text{O}_2$ . The concentrations of  $\text{H}_2\text{O}_2$  are indicated in the figure. In PBS solution without  $\text{H}_2\text{O}_2$ , the PB-modified electrode exhibited a well-defined pair of reversible oxidation-reduction peaks, which corresponded to the redox transitions between Fe(II) and Fe(III) within PB. The oxidation-reduction potentials were 0.12 V and 0.07 V, respectively. The difference between them was 0.05 V, or 50 mV, which was close to the theoretical value of 59 mV for a single-electron transfer process according to the Nernst equation, thus demonstrating the excellent electrochemical reversibility of the PB-modified electrode. Moreover, with increasing  $\text{H}_2\text{O}_2$  concentration, the oxidative peak of PB gradually decreased while the reductive peak grew, substantiating the electrochemical reduction of  $\text{H}_2\text{O}_2$  occurring at the PB-modified electrode [32].



**Figure 5.** The electrochemical characterization of Sensor-Glucose: (A) CVs of PB-modified electrode in 0.1M PBS + 0.1 M KCl, pH 7.4, containing different concentrations of  $\text{H}_2\text{O}_2$ . Potential range  $-0.1$  V to  $0.4$  V; scan rate  $50$  mV/s. (B) Chronoamperometric response of PB-modified electrode in 0.1M PBS + 0.1 M KCl, pH 7.4, to different concentrations of  $\text{H}_2\text{O}_2$ . The concentrations of  $\text{H}_2\text{O}_2$  were  $0.1$ ,  $0.2$ ,  $0.3$ ,  $0.4$ ,  $0.5$ ,  $1.0$ ,  $1.5$ ,  $2.0$ ,  $2.5$ ,  $3.0$ , and  $3.5$  mM, respectively. Applied potential  $0.07$  V; applied time  $60$  s. The inset shows the linear fitting calibration curve. (C) CVs of Sensor-Glucose in 0.1M PBS, pH 7.4, containing different concentrations of glucose. Potential range  $-0.1$  V to  $0.3$  V; scan rate  $50$  mV/s. (D) Chronoamperometric response of Sensor-Glucose in 0.1M PBS, pH 7.4, to different concentrations of glucose. The concentrations of glucose were  $0.5$ ,  $1.0$ ,  $1.5$ ,  $2.0$ ,  $2.5$ ,  $3.0$ ,  $3.5$ ,  $4.0$ ,  $4.5$ ,  $5.0$ ,  $5.5$ ,  $6.0$ ,  $6.5$ , and  $7.0$  mM, respectively. Applied potential  $0.07$  V; applied time  $60$  s. The inset shows the linear fitting calibration curve.

Figure 5B shows the chronoamperometric response curves of the PB-modified electrode for different concentrations of  $\text{H}_2\text{O}_2$ . As the  $\text{H}_2\text{O}_2$  concentration increased, the electrochemical reduction current of the PB-modified electrode steadily rose. The inset

depicts a plot of current response intensity versus  $\text{H}_2\text{O}_2$  concentration. It can be seen that the sensor exhibited a good linear response range for  $\text{H}_2\text{O}_2$  from 0.1 to 3.5 mM, with a sensitivity of  $3.89 \mu\text{A}/\text{mM}$  and a detection limit of  $1.09 \mu\text{M}$  ( $\text{S}/\text{N} = 3$ ). The linear regression equation for this curve is as follows:

$$I (\mu\text{A}) = -3.89 \times c(\text{H}_2\text{O}_2) (\text{mM}) + 0.16 (\mu\text{A}) (R^2 = 0.9979)$$

Figure 5C presents the electrochemical CVs testing of Sensor-Glucose for different glucose concentrations. The concentrations of glucose are indicated in the figure. In the absence of glucose, the CV curve of Sensor-Glucose in PBS exhibited a well-defined pair of reversible electrochemical oxidation-reduction peaks, which corresponded to the electrochemical redox behavior of PB. Similar to the discussion concerning the PB-modified electrode above, the electrochemical oxidation and reduction peaks for Sensor-Glucose in PBS were also found at 0.12 V and 0.07 V, respectively, with the difference between them close to the theoretical value for a single-electron transfer process according to the Nernst equation. This indicated that the state of the electrode was not significantly altered following modification with the GOD/MWCNT-COOH/chitosan membrane. Moreover, upon the addition of glucose, similar to the results discussed for the PB-modified electrode, the electrochemical oxidation peak of Sensor-Glucose gradually diminished, while the electrochemical reduction peak increased. This confirmed the process by which glucose was enzymatically oxidized on Sensor-Glucose to generate  $\text{H}_2\text{O}_2$ , which was then electrochemically reduced at the PB-modified electrode.

Figure 5D displays the chronoamperometric response curves of Sensor-Glucose for varying glucose concentrations. It is evident that the electrochemical current of the sensor continuously increased with escalating glucose concentrations, substantiating the feasibility of glucose electrochemical sensing using this sensor. The inset shows the calibration curve for the sensor's response to different glucose concentrations. The fitted linear range is 0.5 to 7 mM, with a sensitivity of  $2.15 \mu\text{A}/\text{mM}$ , and a detection limit of  $1.71 \mu\text{M}$ . The regression equation for this curve is as follows:

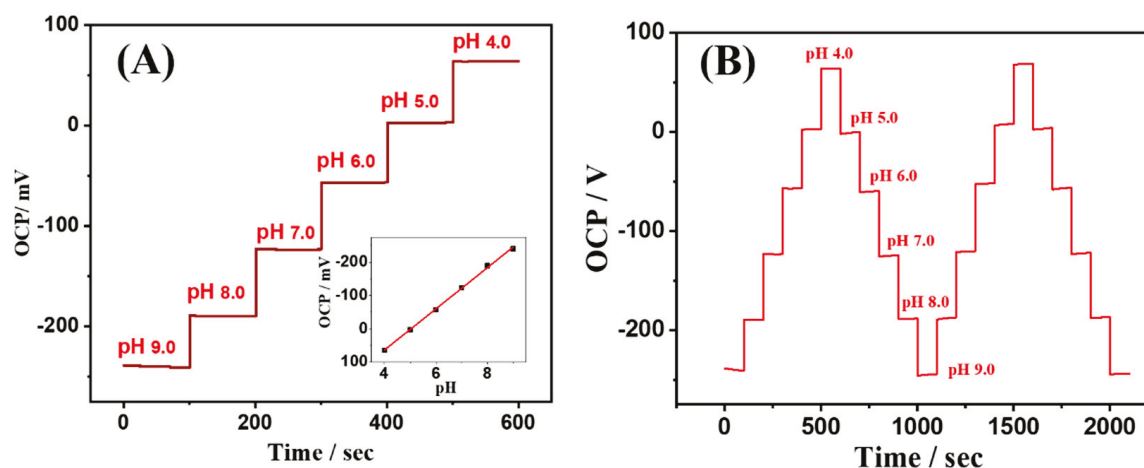
$$I (\mu\text{A}) = -2.15 \times c(\text{glucose}) (\text{mM}) - 0.28 (\mu\text{A}) (R^2 = 0.9984)$$

The results of the reusability and anti-interference performance tests for Sensor-Glucose are depicted in Figure S3, showcasing its excellent reusability and robust anti-interference capabilities.

### 3.2.3. Sensor-pH

To obtain different pH values of the tested solution, 0.2 M NaOH was added to the Britton–Robinson buffer solution to adjust the pH to 4.0, 5.0, 6.0, 7.0, 8.0, and 9.0, respectively. The open-circuit potential (OCP) of the Sensor-pH was tested in each of these solutions, with each OCP measurement lasting for 100 s. As shown in Figure 6A, the results indicate that as the pH decreased from 9.0, the OCP of the Sensor-pH rose from  $-240 \text{ mV}$ , reaching  $64 \text{ mV}$  at  $\text{pH} = 4.0$ . The inset demonstrates a linear relationship between the sensor's OCP and the measured pH, with a slope of  $-60.5 \text{ mV}/\text{pH}$ , closely approaching the theoretical value of  $-59 \text{ mV}/\text{pH}$  predicted by the Nernst equation for OCP–pH relationship.

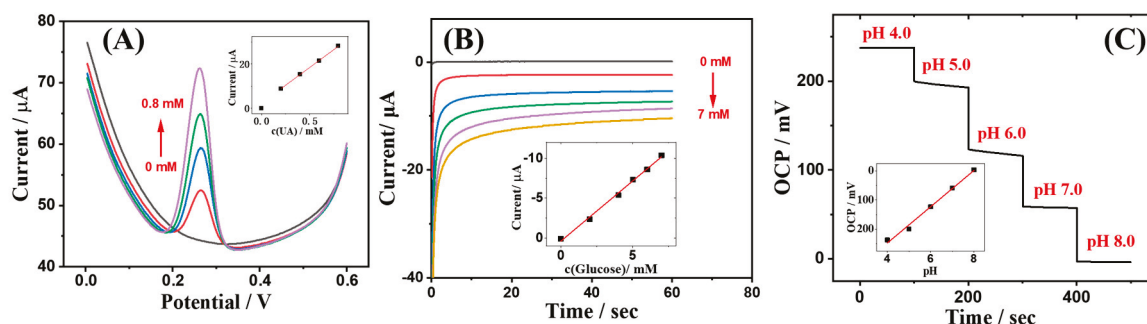
To evaluate the repeatability of the Sensor-pH, the sensor was immersed in solutions with varying pH values ranging from 9.0 down to 4.0, after which the pH of the solutions was raised back up to 9.0, and the OCP of the Sensor-pH was measured across all the solutions. The results, depicted in Figure 6B, show that the Sensor-pH exhibited nearly identical OCP responses before and after each pH change, indicating the excellent reusability and repeatability of the sensor under continuous alterations in the solution pH.



**Figure 6.** (A) The open-circuit potential response of the Sensor-pH to different pH values. The inset shows the linear relationship between the sensor's OCP and the measured pH. Each OCP for pH was measured for 100 s. (B) Repeatability of the Sensor-pH when the pH of the solution undergoes continuous alterations.

### 3.3. Electrochemical Sensing for Artificial Interstitial Fluid Samples

To assess the practical application potential of the jellyfish-shaped sensor, its electrochemical sensing performance for biomarkers in AISF was initially examined. As shown in Figure 7A, upon immersion of the sensor in AISF and the subsequent addition of varying concentrations of uric acid, the sensor demonstrated a favorable electrochemical response to uric acid within a concentration range of 0 to 0.8 mM via DPV. Moreover, a conspicuous electrochemical oxidation peak appeared at a potential of 0.27 V. The inset illustrates a calibration curve of peak current versus uric acid concentration, revealing a strong linear relationship with a response slope of 32.05  $\mu\text{A}/\text{mM}$  and an  $R^2$  value of 0.9996.



**Figure 7.** The electrochemical sensing performance of the jellyfish-shaped sensor. (A) DPVs of the sensor to UA. The concentration of UA was 0, 0.2, 0.4, 0.6, and 0.8 mM, respectively. Potential range 0 to 0.6 V; amplitude 0.05 V; pulse width 0.05 s. (B) Chronoamperometric response of the sensor to glucose. The concentration of glucose was 0, 2, 4, 5, 6, and 7 mM, respectively. Potential applied 0.07 V; applied time 60 s. (C) OCP response of the sensor to different values of pH. The pH value tested is indicated in the figure.

Similarly, the electrochemical sensing capability of glucose was evaluated. As depicted in Figure 7B, an increase in the reduction current response was observed as the glucose concentration rose. The inset presents the relationship between the current response and glucose concentration over the range of 0 to 7 mM, evidencing a good linear response of the sensor to glucose concentrations, with a slope of  $-1.51 \mu\text{A}/\text{mM}$  and an  $R^2$  value of 0.9964.

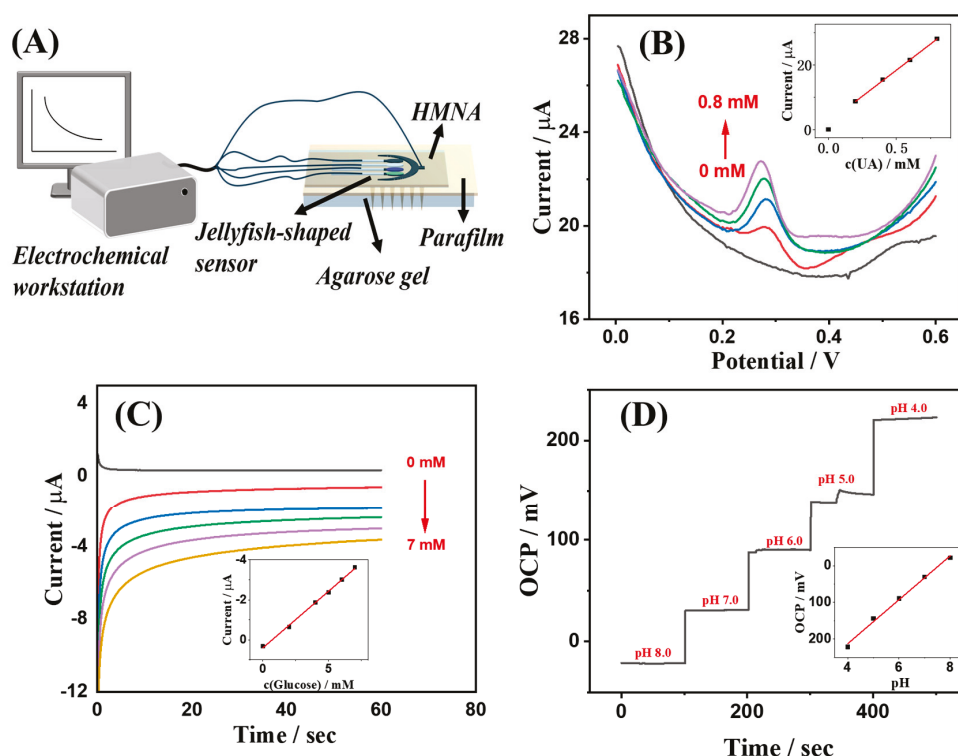
Lastly, the OCP response of the jellyfish-shaped sensor to a pH range of 4.0–8.0 in the AISF was tested, as shown in Figure 7C, where the sensor exhibited a discernible stepwise response to different pH levels. The inset figure displays the linear correlation between the

obtained OCP and pH, with a slope of  $-62.2\text{ mV/pH}$ , closely approximating the theoretical value predicted by the Nernst equation for the OCP–pH relationship.

Collectively, the sensor demonstrates an excellent sensing performance to uric acid, glucose, and pH in AISF. It is worth mentioning that the sensor's sensing range covered the physiological concentration ranges of these three biomarkers (UA:  $0.12\sim0.45\text{ mM}$  [18], glucose:  $3.6\sim6.0\text{ mM}$  [18,33], pH:  $6.60\sim7.60$  [20]). These findings underscore the immense application potential of this sensor.

#### 3.4. Electrochemical Sensing in Simulated Epidermis

To evaluate the stratum corneum penetration and electrochemical sensing performance of biomarkers of the HMNA-integrated jellyfish-shaped electrochemical sensor system, a puncture experiment was conducted using parafilm to simulate the human stratum corneum and a 5 wt% agarose hydrogel to mimic epidermis. The schematic diagram of the experimental setup for the test is shown in Figure 8A. The preparation of 5 wt% agarose hydrogel was as follows: 1 g agarose was dissolved in 20 mL deionized water, and the mixture was heated to  $105\text{ }^{\circ}\text{C}$  until the agarose was fully dissolved, yielding a clear transparent solution, which was then allowed to cool to room temperature for use. In the experiment, a certain pressure applied by a finger on the backside of the HMNA enabled it to easily penetrate the simulated stratum corneum. Subsequently, the jellyfish-shaped electrochemical sensor was attached to the back of the HMNA to conduct the corresponding electrochemical measurements. During the testing process, AISF containing biomarkers with appropriate concentrations was added beneath the simulated epidermis for electrochemical sensing.



**Figure 8.** HMNA-integrated jellyfish-shaped electrochemical sensing system for biomarker sensing in simulated epidermis. (A) The schematic diagram of the experimental setup for the test. (B) DPVs for UA sensing. The concentration of UA was 0, 0.2, 0.4, 0.6, and 0.8 mM, respectively. Potential range 0 to 0.6 V; amplitude 0.05 V; pulse width 0.05 s. (C) Chronoamperometric response for glucose sensing. The concentration of glucose was 0, 2, 4, 5, 6, and 7 mM, respectively. Potential applied 0.07 V; applied time 60 s. (D) OCP response for pH sensing. The pH value tested is indicated in the figure.



Figure 8B illustrates the electrochemical sensing results of the sensing system for uric acid, where it is evident that the DPV peak current intensity of the sensing system for uric acid concentrations within the physiological ranges beneath the simulated epidermis increased with rising uric acid levels. The inset displays a calibration curve of peak currents from DPV responses to uric acid concentrations, exhibiting a strong linear correlation.

Figure 8C depicts the electrochemical sensing outcomes for glucose within the simulated epidermis, revealing a proportional relationship between the system's current response and glucose concentrations under physiological conditions. The inset shows the relationship between response currents and glucose concentration, also demonstrating good linearity.

Figure 8D presents the pH-sensing results of the system in the simulated epidermis, with the OCP of the sensing system varying linearly as the pH shifted from 4.0 to 8.0. The inset provides a linear relationship graph of OCP versus pH.

Collectively, these results confirm that the HMNA-integrated jellyfish-shaped electrochemical sensor system demonstrated excellent electrochemical responsiveness to uric acid, glucose, and pH under simulated epidermal conditions, exhibiting favorable linear responses for the physiological concentrations of these biomarkers. This validates the potential application of this sensing system in real epidermal scenarios.

#### 4. Conclusions

In this study, we developed and validated an HMNA-integrated jellyfish-shaped electrochemical sensor system capable of concurrently measuring uric acid, glucose, and pH in a simulated epidermal. The system's sensitivity and linearity across physiological concentrations affirm its viability for the monitoring of biomarkers related to diabetes, gout, and metabolic health. The sensor's design overcomes the challenges associated with conventional sampling methods and paves the way for advanced wearable health monitoring technologies. By enabling the real-time and multiplexed analysis of critical biomarkers, this innovation contributes to the advancement of personalized medicine and facilitates early disease detection and management.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/s24123729/s1>, Figure S1: The cyclic voltammograms of (A) PB electrodeposition, and (B) polyaniline electropolymerization; Figure S2: The reusability and anti-interference performance tests for Sensor-UA. DPV tests: Potential range 0 V to 0.3 V, amplitude 0.05 V, pulse width 0.05 s. (A) The sensor was scanned for 10 times in PBS, pH 7.4, containing 0.5 mM UA. (B) Anti-interference test of the Sensor-UA for common physiological interferences. Glu: glucose; AA: ascorbic acid; Cr: Creatinine; LA: lactic acid; Figure S3: The reusability and anti-interference performance tests for Sensor-glucose. Chronoamperometric tests: Applied potential 0.07 V, applied time 60 s. (A) The sensor was scanned for 14 times in PBS, pH 7.4, containing 2.5 mM glucose. (B) Anti-interference test of the Sensor-glucose for common physiological interferences. UA: uric acid; AA: ascorbic acid; Cr: Creatinine; LA: lactic acid.

**Author Contributions:** Conceptualization, F.L. and J.-L.M.; Methodology, W.S. and Z.W.; Software, Y.S.; Formal analysis, W.S. and Y.W.; Investigation, F.L., J.S. and Y.C.; Data curation, F.L. and Y.S.; Writing—original draft, Z.L.; Visualization, Y.S., Z.F. and Y.H.; Supervision, Z.L. and Z.Z.; Project administration, Z.L. and Z.Z.; Funding acquisition, Z.L. All authors have read and agreed to the published version of the manuscript.

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Review

# Biocompatible Electrical and Optical Interfaces for Implantable Sensors and Devices

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**Abstract:** Implantable bioelectronics hold tremendous potential in the field of healthcare, yet the performance of these systems heavily relies on the interfaces between artificial machines and living tissues. In this paper, we discuss the recent developments of tethered interfaces, as well as those of non-tethered interfaces. Among them, systems that study neural activity receive significant attention due to their innovative developments and high relevance in contemporary research, but other functional types of interface systems are also explored to provide a comprehensive overview of the field. We also analyze the key considerations, including perforation site selection, fixing strategies, long-term retention, and wireless communication, highlighting the challenges and opportunities with stable, effective, and biocompatible interfaces. Furthermore, we propose a primitive model of biocompatible electrical and optical interfaces for implantable systems, which simultaneously possesses biocompatibility, stability, and convenience. Finally, we point out the future directions of interfacing strategies.

**Keywords:** implanted sensor; electrical interface; optical interface; biocompatibility; human–machine integration

## 1. Introduction

In an era of rapidly advancing biotechnology and electronics, the integration of humans with machines has become a hot topic in the research community, showing immense application potential in interdisciplinary fields such as neuroscience, rehabilitation medicine, and bioengineering [1–6]. The current instances of human–machine integration can be divided into two main categories: invasive systems and noninvasive systems. The former require relatively complicated surgical procedures to implant sensing or actuating modules into the human body, increasing the risk of infection. The latter, however, utilize external devices, involving wearable devices to realize the human–machine interaction, at the expense of an inferior signal quality.

During this trend, implantable sensors and devices have undergone unprecedented revolutionary breakthroughs, offering promising applications across diverse domains, from diagnostics to therapeutics. In terms of medical assessment, there are numerous methods using electrodes and probes to detect and analyze physiological signals, including electrocorticography (ECoG) [7,8], micro-electrocorticography ( $\mu$ ECoG) [9,10], electroencephalography (EEG) [11,12], electromyography (EMG) [13,14], and others [15–19], which provides an important means to gain a deeper understanding of brain and muscle activity. Similarly, to treat diverse functional diseases, a great many implantable systems have been approved, such as cardiac pacemakers for cardiac dysfunction and cochlear implants for

hearing impairment, significantly improving the quality of life of patients and bringing new possibilities to the medical field [20–22].

Establishing stable, effective, and biocompatible interfaces between artificial machines and living tissues plays a vital role in implantable bioelectronics since the interface technologies inevitably determine the transmission of experimental signals, as well as the responses of surgical wounds. Hereinafter, the term “electrical interface” refers to an electrical feedthrough mounted onto a piece of skin or bone, usually with multiple channels connecting the artificial sensors or devices implanted into live bodies to external instruments so that electrical signals can be read out or sent in. The term “optical interface” refers to an optical feedthrough which allows light to pass through freely from either side. The following reviews the different kinds of interfacing modules in implantable systems, encompassing physical tethers and other specially shaped interfaces. We also discuss the selection of the perforation site, the fixing strategy for interfaces, the precautions with long-term indwelling, and the properties of wireless systems as a comparison. Moreover, we present a versatile model of a multi-functional interface that is biologically friendly and conveniently usable.

## 2. Tethered Interfaces

Connecting devices *in vitro* and/or *in vivo* in laboratory versions of implantable systems commonly relies on physical tethers that are convenient to operate and available for purchase. For instance, copper wires are frequently used in neuroscience research, whereby anisotropic conductive film (ACF) or silver paste one end of the wire is adhered to an electrode for measurement or stimulation and the other to an external instrument for data processing or signal controlling. Likewise, commercial optical fibers and fluidic tubes serve as an interfacing module in optogenetic experiments and drug delivery, respectively.

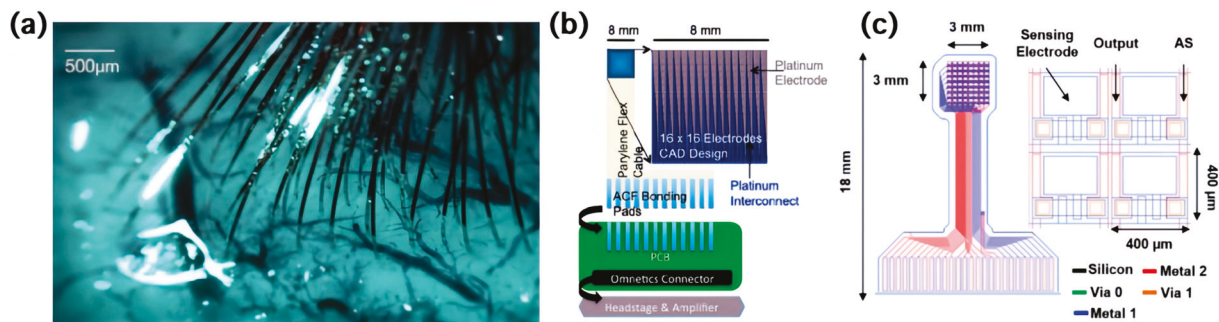
### 2.1. Multi-Channel Interfaces

The properties of the physical tethers determine the signal quality and quantity to a large degree, so using a single commercial cable may not be the optimal interface strategy for implantable systems in more complicated contexts.

One trend in interface research is scaling the number of channels to meet the pressing need for increased signal density. As is depicted in Figure 1a, a customized neurosurgical robot is built to rapidly and reliably insert arrays of 96 electrode threads. The arrays are packaged into a small device equipped with other sensing and processing modules, making electrophysiological recordings over 3000 channels. In addition to insertion on the surface of the cerebral cortex, the system can also be positioned and implanted into multiple brain regions to achieve a broader range of neural signal recording. The main substrate and medium used in this ultra-thin polymer probe is polyimide (PI), whose dimensions and composition match the material properties of brain tissue, allowing for long-term implantation in living organisms [23]. But the above interfacing strategy is not generally applicable. The individual cabling of each channel is undesirable in that it requires opening wounds across large areas to arrange the wires in a distributive pattern or extremely delicate surgical techniques for small-interval arrays. Researchers are thus exploring ways to fabricate multi-channel cables. The mainstream process is metal deposition and etching on thin film substrates. In one example, platinum is e-beam-evaporated and patterned in parylene using oxygen plasma reactive ion etching (Figure 1b). This cable is monolithically integrated with the electrode array at the wafer level and thermo-compression-bonded to a fanout plastic circuit board (PCB) in an ACF flex process, forming a 256-channel  $\mu$ ECoG measurement system. The integration of the cable with the electrode array allows for precise positioning of the electrodes in the target brain regions, enabling accurate and localized neural recordings. The thermo-compression bonding process ensures a secure and reliable connection between the parylene cable and the fanout PCB, enhancing the overall stability and performance of the  $\mu$ ECoG system. The use of ACF technology facilitates efficient signal transmission and data acquisition across all 256 channels [24]. Figure 1c shows an



improved structure: a double-layer metal interconnected cable that realizes a great rise in the channel count to the kilo-scale and mega-scale. During the implantation process, the interconnected cables outside the electrode array are bent at a  $90^\circ$  angle with a bending radius of less than 2 mm to reduce the formation of tiny cracks during cable handling. Furthermore, to enhance the stability of the interconnected cable region, a  $12.5\ \mu\text{m}$  thick PI protective layer is added to the top surface of the array cables. It is notable that in this work, thermally grown silicon dioxide serves as a robust, bendable, and ultrathin biofluid barrier [25,26].



**Figure 1.** Different layouts of cables in multi-channel interfaces. (a) Arrays of electrode threads inserted into the cerebral cortex [23]; (b) schematic drawing of a 256-channel  $\mu\text{ECoG}$  measurement system [24]; (c) schematic drawing of a double-layer metal interconnected cable [25].

Recently, some groups have adopted new methods to establish multi-channel interfaces, involving 3D printing [27], liquid metal injection [28], and thermal drawing processes [29], but these methods are still in an embryonic stage, where one cable contains tens of channels and specialized cables are only feasible for set experimental objectives.

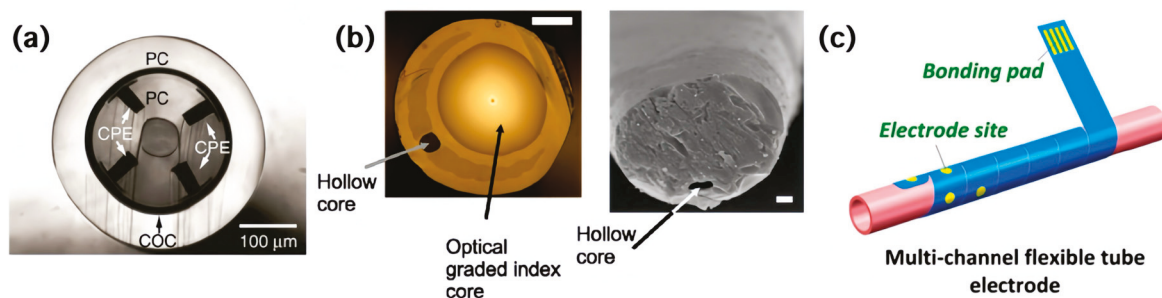
## 2.2. Multi-Functional Interfaces

Other interfaces of recent interest are concerned with integrating multiple functions, such as electrical stimulation and photometric recording [30–32]. Through innovation in the constructional design and manufacturing processes, a minimally invasive interface is able to transmit two or more separate signals simultaneously.

The concentric preform, as depicted in Figure 2a, consists of a central hollow microfluidic channel surrounded by a polycarbonate (PC) cylindrical waveguide and four conductive polyethylene (CPE) electrodes. The preform is subjected to the thermal drawing process, resulting in a micro-diameter fiber, with its dimensions reduced by a factor of approximately 100. To further reduce its dimensions, dichloromethane is used to selectively etch the outer PC cladding, exposing the inner components of the fiber. These multifunctional fiber probes have been implanted into the medial prefrontal cortex (mPFC) of mice. They interact with the external world by connecting to external circuit boards and optical fibers, realizing optogenetic stimulation, neural recording, and drug delivery. These probes form stable brain–machine interfaces in the mouse brain, allowing for long-term implantation and functional maintenance and facilitating extended manipulation and analysis of the neural circuits [29].

Figure 2b demonstrates a different geometry of the fiber instead of a concentric structure. It contains two cores in a silica inclusion tube: a graded refractive index optical core doped with  $\text{GeO}_2$  for light delivery and collection and a silica capillary hole filled with an electrolyte solution (1–3 M NaCl) to record electrical activity. The tapered end of the optical fiber probe is typically implanted into the intact brain tissue of a mouse, while the other end is connected to a photomultiplier tube (PMT) via a multimode optical fiber, undertaking the transmission, collection, and electrical recording of light [33]. Along with these cylindrical fibers having been inspired by the stack-and-draw method, exploiting their surface structure to develop a multi-functional interface has also been validated. For

example (Figure 2c), wrapping a sandwich-structured parylene electrode onto the surface of a PI capillary enables omnidirectional electrical interaction with tissue, as well as oriented nutrition factor delivery. The microelectrode structure is composed of a hollow tubular core acting as a fluidic channel and electrode sites distributed on the surface of the tubular structure. This design allows for contact with tissue from any direction. The microelectrode has been implanted into the gastrocnemius (GA) and tibialis anterior (TA) muscles of a rat, implementing dynamic electrophysiological recording and fluidic drug delivery. The electrical stimulation sequence and electrophysiological signals could be imported and extracted through the electrode sites, facilitating bidirectional communication with the surrounding tissue [34].



**Figure 2.** Different geometric designs of tethers in multi-functional interfaces. (a) Cross-sectional optical image of a fiber probe integrating one microfluidic channel, four electrodes, and a surrounding waveguide [29]; (b) photomicrograph of the dual-core fiber (left) and Scanning Electron Microscope micrograph of the tip (right) [33]; (c) schematic drawing of the flexible tube with electrodes distributed on the surface [34].

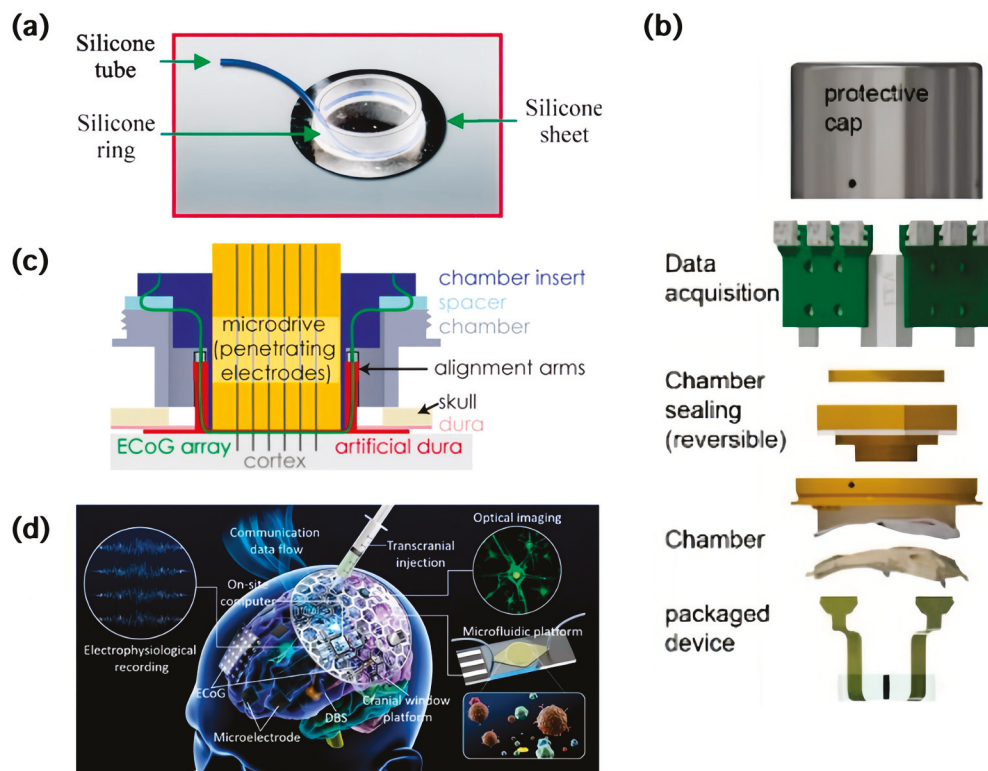
### 3. Non-Tethered Interfaces

Tethered interfaces concentrate mainly on signal transmission but lack consideration of the tissues around. In order to establish better contact that is mechanically secure and biologically friendly, interfaces that are untethered have emerged in recent years. One natural and popular design is to substitute artificial electrical systems for artificial human body parts, in which case their biomimetic geometry distributes the mechanical stress around the interface and inhibits the impact of tissue regeneration. For those whose target organs are far from the surface of the body, additional thought should be given to the inner channel and the percutaneous structure.

#### 3.1. Artificial Dura Systems

An artificial dura system is one of the broadly employed interfaces for implants that have direct contact with the brain or spinal cord. It can be traced to cranioplasty, a centuries-old surgical procedure for cranial defect repair [35]. Inspired by bone grafts for cranioplasty, artificial dura systems utilize metals such as titanium to replace the skull, supporting the inner devices and protecting the brain. To satisfy the demand of optical imaging, the past two decades have witnessed the development of a transparent artificial dura system, which typically constitutes dural substitute and functional modules, with glass cranial windows positioned over the top of the implanted devices [36–38].

Figure 3a illustrates an early silicone design consisting of a sheet to cover the cortical surface, a ring to block the re-growth of the cutting edge of the natural dura, and a tube to let different solutions be flushed over the cortex. A glass coverslip serves as a cranial window, and the whole device is shielded by a metal chamber and a metal cap. This system helped record intrinsic or voltage-sensitive dye signals by means of optical imaging in an experiment of more than a year duration, during which the tested monkeys and the implanted substitute were both in superb condition, with no evidence of damage [39].



**Figure 3.** Examples of artificial dura systems. (a) A silicone dura substitute for long-term optical imaging [39]; (b) schematic drawing of a chamber-based system for neural activity [25]; (c) schematic drawing of a chamber system that simultaneously records  $\mu$ ECoG, LFP, and spiking activity [40]; (d) a proposal for large-area multi-functional artificial dura system [41].

Combined with modern electronic technologies, artificial dura systems have gradually developed into complex chamber systems that integrate signal measurement and processing. A chamber-based neurotechnology device testing approach is portrayed in Figure 3b. The dura is replaced with one containing embedded ECoG arrays, and the chamber sealing specializes the cable routing, which avoids extra surgical implantation and allows for rapid test cycles with reversible seals, instead of the traditional techniques of repeating the animal preparation, device placement, and data acquisition. Neural activity is successfully observed in the form of evoked potentials by the optimized system when the subject experiences full-field visual stimuli or performs delayed-reach tasks [25]. Figure 3c shows the design of a chamber to house a silicone artificial dura with custom  $\mu$ ECoG arrays and a commercially available micro-drive system with penetrating electrodes, where these two parts are precisely aligned. Furthermore, PEEK plastic is used to maintain the imaging compatibility, and the system is affixed to the skull via MetaBond and dental acrylic. It is notable that  $\mu$ ECoG, LFP, and spiking activity are simultaneously recorded via one system, and the modular design can incorporate other functional hardware in principle [40].

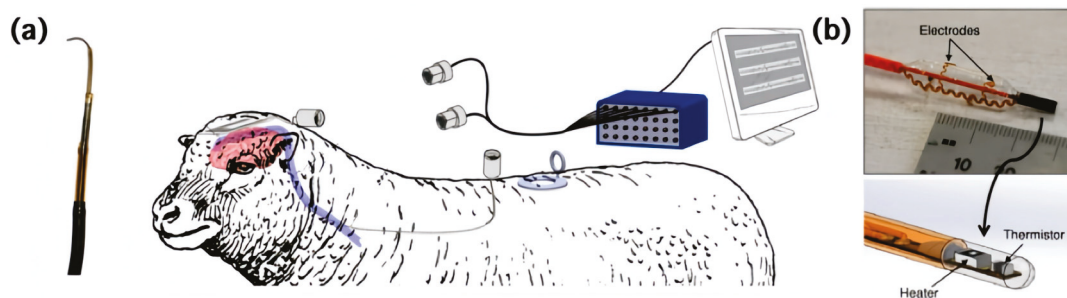
Figure 3d presents an ideal model of an artificial dura system for long-time implantation, which involves a variety of smart built-in modules, including micro sensor nodes, data processing units, and wireless communication modules [41]. Taking the first step towards this model, a primitive overlaid cranial window based on 3D printing was engineered and implanted into mice for 21 weeks. In this prototype, the Ti honeycomb is coated with polydimethylsiloxane (PDMS), allowing for optical imaging and transcranial injection [42].

### 3.2. Catheter-Based Systems

Catheter-based devices are another type of universally applied interface for medical applications such as endoscopic surgery and catheterization procedures. A conventional catheter-based device in medicine is composed of tubes to give drugs or take samples and

sheaths or balloons to provide the mechanical force for fixation or dilation [43]. So far, some progress has been made in enhancing their procedural security and improving the device stability [44–46]. But previous systems have been focused on the capability to infuse or drain fluids and have neglected the possibility of realizing signal detection.

Recent advances in catheter-based systems have added electrical modules, making them more intelligent and controllable. Figure 4a introduces an endovascular system which can be simply summed up as a passive stent-electrode recording array wrapped in coaxial catheters. The microwire and outside catheters are navigated to the target vessel using the Seldinger technique and digital subtraction angiography, tunneled subcutaneously to a custom-made hermetic connector, which is secured to a muscle, and exiting the skin into a percutaneous micro circular plug. This work reported the recording of vascular electrocorticography in living sheep for up to 190 days [47]. In Figure 4b, the arterial sheaths facilitate the deployment of a balloon-based catheter system into the femoral artery. The system is built on a flexible balloon substrate that gently makes contact with the surrounding tissues when inflated with cold saline. The electrodes and flow sensors positioned on the catheter are connected in wavy geometry using a copper or gold pad between two PI layers. This system offers a way to evaluate vessel health, which was proven by signal acquisition and analysis of the blood flow in anesthetized farm swine [48].



**Figure 4.** Examples of catheter-based systems. (a) Image of a coaxial catheter system including sheaths and microwire and schematic drawing of the animal experiment [47]; (b) optical image of a balloon-based catheter system and expanded drawing of the flow sensor on the tip [48].

## 4. Further Discussion

### 4.1. Perforation Site

The selection of the perforation site is a critical consideration for the design of interfaces, depending on the requirements of the devices and the conditions of the subjects. Considering the signal attenuation with distance in wired transmission, the interface usually pierces the nearby tissues around the target organ to ensure high-quality interaction between the internal and external devices. This kind of perforation not only simplifies the surgical procedure for implants owing to concentrated incisions but also diminishes the risk of complications, as the implants being in proximity to the target organ avoids other important vulnerable structures such as the nerves and blood vessels. Voluntary actions of the subjects influence the selection of the perforation site as well. In many testing experiments, the interfaces are placed on the head or the back of an animal so that they do not impede small-scale movement nor will be displaced by frequent touching [49]. Faced with the chosen perforation sites, the interfaces utilize tailored designs. For example, an interface on the abdomen is expected to be softer and more stretchable than that on the skull on account of biomechanical stresses.

In summary, the selection of the perforation site involves a comprehensive assessment of signal transmission, surgical feasibility, subject behavior, and anatomical considerations. By carefully considering these factors and employing tailored design approaches, implantable interfaces can achieve the optimal performance and integration with living tissues.



#### 4.2. Fixing Strategy

An ignored problem for interfaces crossing living tissues is the technique for fixing the piercing part into the biological tissue. For tests where the experimental animals are continuously anesthetized or tied to a pad, the skin incisions are closed with sutures after subcutaneous implantation, and the tether is thus constrained at the seam [50–53]. Nevertheless, this method is inapplicable when the test is conducted on conscious unrestrained animals, in which case the interface will easily fall off. Screws are also used, but this method is only suitable for rigid interfaces and perforation sites like the skull [54,55]. A more common solution is to apply dental or bone cement to cover the contact area between the interface and tissue. The cement, on the one hand, possesses high tensile strength, which effectively prevents displacement of the interfaces [56]. On the other hand, it protects the surrounding tissue from invaders and prevents the release of exudate thanks to its good sealing ability. Since the interface has direct contact with the surgical wound, an ideal interfacing strategy is supposed to help reduce inflammation or rejection. Therefore, cement with antibiotics has been employed to ensure the duration of live experiments [57]. Despite all these advantages of cement, it has a fatal flaw: it is relatively hard compared to soft tissues, which may cause acute injury such as tissue displacement and glial activation, leading to both tissue and device damage [58,59].

To address these challenges, novel fixation strategies are being explored. These include the development of softer, more biocompatible materials that can securely anchor the interface while minimizing tissue trauma. Additionally, advancements in bioadhesive technologies aim to provide strong yet flexible adhesion to living tissues without causing undue harm. By developing solutions that balance secure attachment with tissue compatibility, researchers can enhance the safety and effectiveness of implantable bioelectronics.

#### 4.3. Long-Term Indwelling

The testing animals are often killed after temporary experiments to further examine their tissues. But when it comes to wired systems for constant monitoring, the implantable devices and the surface interfaces must have prolonged retention *in vivo*, which may lead to device failure and subject damage. This issue can be resolved by choosing a proper material that is compatible with the tissues to isolate the inner module from bodily fluids [60]. Silicone materials, including PDMS, have been widely used, and other emerging materials such as metal–organic frameworks also demonstrate superior performance in device manufacturing [61].

Furthermore, the stability and connectivity of each module is crucial because any irregularity will probably result in surgery to replace the whole system. Recent advancements offer promising solutions to improve the stability and connectivity of implantable systems. For example, researchers have developed biphasic, nano-dispersed interfaces by thermally evaporating conductive nanoparticles into an elastic substrate. This innovative approach provides a plug-and-play connection between different modules, ensuring robustness and flexibility. Such interfaces have demonstrated reliable performance in detecting subcutaneous compound muscle action potential [62], showcasing their potential to enable long-term retention in living tissues while maintaining connectivity with external devices.

By adopting the novel approaches described above, researchers can mitigate adverse outside influences and enhance the reliability and longevity of implantable devices for continuous monitoring applications. These advancements facilitate safer and more effective long-term studies in both animal models and human subjects.

#### 4.4. Wireless Strategy

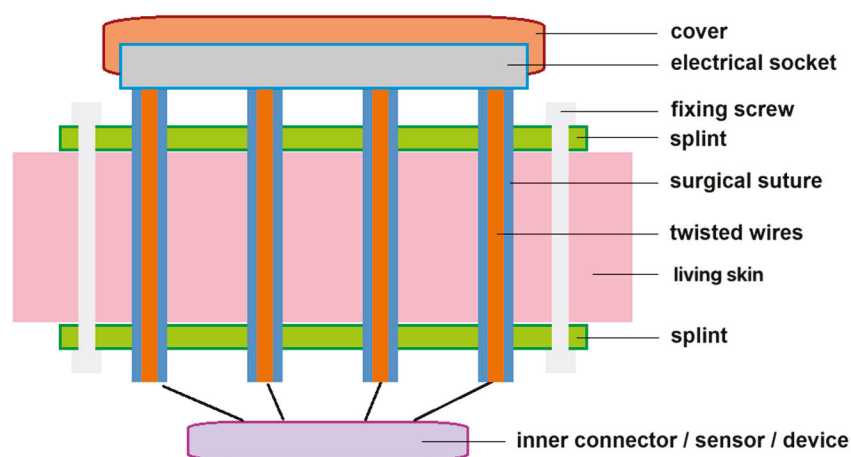
The interfaces introduced above, however, prompt long-term opening of wounds, increasing the danger of infection. Other complications with wires like thrombosis and organ malfunction are also potential hazards that have received considerable attention [63,64]. In addition, wired connection to external devices restricts the behaviors of the test subjects, especially their social interaction and activity level [65]. By contrast, wireless implantable



systems minimize these negative environmental impacts because of the postoperative suture and greatly reduce mechanical constraints so that the subjects are free to move around [66]. As a well-known example, Neuralink displayed a live pig with a coin-sized device inserted into its brain on a webcast on 28 August 2020 [67]. This device could detect neural spikes and send wireless signals to a nearby computer, and the pig could freely eat or sniff on camera. After these early animal experiments, this year, Neuralink claimed to have implanted a brain chip into a human for the first time, but more detailed information about this trial still remains confidential and undisclosed, which has triggered heated controversy about its safety and reliability [68,69]. Although wireless medical systems have raised high expectations and have already been put into practical use, there still exist some unaddressed tasks [70]. For one thing, living tissues pose obstacles to wireless communication, compelling researchers to explore alternative methods for high-efficiency transmission [71,72]. For another, wireless power transfer approaches need further optimization to completely replace implanted batteries, which have a limited lifespan and entail subsequent replacement [73,74].

## 5. A Proposal for Multi-Functional Interfaces

We present here a primitive approach to a multi-functional electrical interface for living tissues. A cross-sectional image of its central part is shown in Figure 5. The overall structure can be described as two pieces of splint embedded with an array of conductive twisted microwires. The splints are made of biocompatible material to prevent inflammation or rejection of the tissues in direct contact with the interface. The core of each surgical suture is a pair of two twisted conducting microwires (Cu, Au, or Ag), which can also be replaced by an optical micro-fiber. The two splints are fixed together with thin metallic screws (made of Ti or stainless steel). The external devices can incorporate wireless technology by integrating processing modules into the socket casing of this device, further enhancing the function of this device. To prevent wear and tear of the signal channels, a sealing and insulating cover is placed over the interface when the system is in idle status. Applications of this interface are not limited to soft tissues such as the skin. It can also be applied to harder sites such as bones through a resection–implantation approach.



**Figure 5.** A schematic drawing of a multi-functional transdermal interface.

## 6. Conclusions

The above reviews the recent developments in interfacing technologies for implantable bioelectronics. From the structural design to the selection of materials and processes, every aspect has a crucial impact on the efficacy and longevity of the interface. While tethered interfaces offer stability and signal fidelity, non-tethered interfaces such as artificial dura systems and catheter-based systems present innovative solutions for specific applications. However, there are challenges that necessitate concerted and continual efforts.

The selection of the perforation site for interfaces is still in the exploratory stage, aiming to meet the functional requirements of a system while minimizing damage to the organism. We expect that in the future, through the use of imaging techniques and computational modeling, researchers will be able to optimize the decision-making process, mitigating risks to surrounding tissues and structures during the surgical procedure.

The existing fixing strategies at the piercing site also need to be improved upon to achieve non-toxicity to the tissues and reduce infections caused by interactions between internal and external substances. Advances in materials science and bioengineering hold good prospects for developing adhesives and sealants that provide robust fixation while promoting tissue integration and reducing inflammatory responses.

Considering the long-term indwelling of the interfaces, the demand for biocompatible materials, sealing techniques, and connecting methods remains paramount. Novel manufacturing processes, including nanofabrication, offer precise control over the design of the interfaces, ensuring their prolonged retention in vivo.

Moreover, although wireless communication and powering provide assistance to implantable systems, wireless interfaces cannot completely replace wired ones for the time being. Problems such as signal attenuation, tissue interference, and power efficiency continue to pose barriers to seamless integration with implantable devices.

Finally, we present a versatile multi-functional interface model, featuring two micro splints embedded with an array of innovative tethers. It utilizes biocompatible materials to prevent tissue rejection, and its tether design enhances its mechanical strength and facilitates secure communication with external devices.

As the research progresses, interdisciplinary collaboration and technological innovation will be key to overcoming the existing challenges. By leveraging developments in materials science, biotechnology, and electronics, future interfacing technologies may unlock the full potential of implantable bioelectronics. This will pave the way for seamless integration with implantable devices, enabling real-time monitoring of health status, targeted therapy delivery, and improved overall quality of life. By focusing on the development of advanced interfacing technologies, we can overcome the existing challenges and usher in a new era of medical innovation that will benefit patients worldwide.

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## Review

# Advancements in Polymer-Assisted Layer-by-Layer Fabrication of Wearable Sensors for Health Monitoring

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**Abstract:** Recent advancements in polymer-assisted layer-by-layer (LbL) fabrication have revolutionized the development of wearable sensors for health monitoring. LbL self-assembly has emerged as a powerful and versatile technique for creating conformal, flexible, and multi-functional films on various substrates, making it particularly suitable for fabricating wearable sensors. The incorporation of polymers, both natural and synthetic, has played a crucial role in enhancing the performance, stability, and biocompatibility of these sensors. This review provides a comprehensive overview of the principles of LbL self-assembly, the role of polymers in sensor fabrication, and the various types of LbL-fabricated wearable sensors for physical, chemical, and biological sensing. The applications of these sensors in continuous health monitoring, disease diagnosis, and management are discussed in detail, highlighting their potential to revolutionize personalized healthcare. Despite significant progress, challenges related to long-term stability, biocompatibility, data acquisition, and large-scale manufacturing are still to be addressed, providing insights into future research directions. With continued advancements in polymer-assisted LbL fabrication and related fields, wearable sensors are poised to improve the quality of life for individuals worldwide.

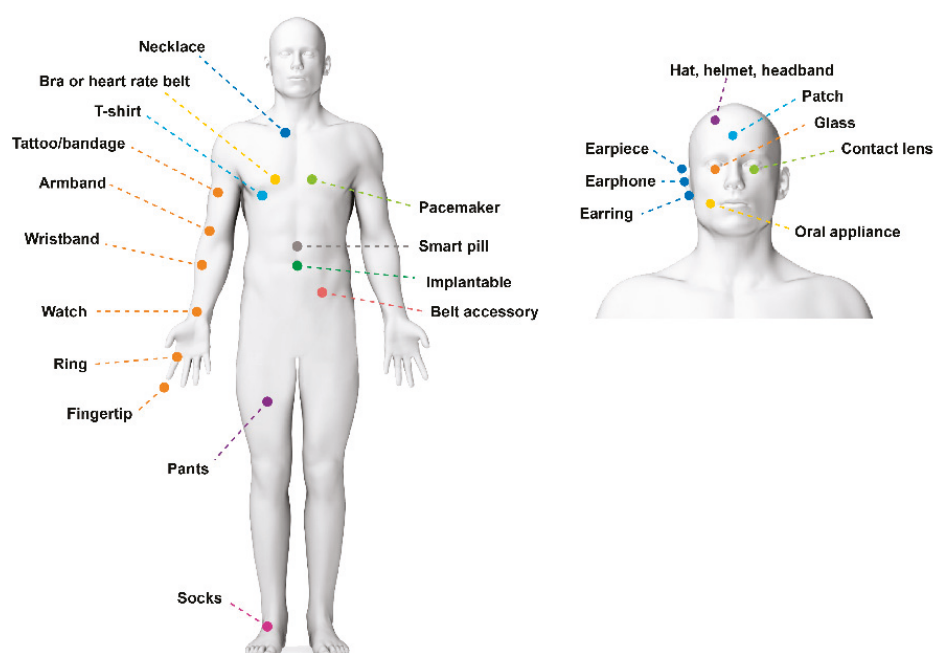
**Keywords:** LbL self-assembly; biocompatibility; stimuli-responsive polymers; personalized healthcare; continuous monitoring

## 1. Introduction

The rapid advancements in technology and the increasing prevalence of chronic diseases have fueled the demand for wearable sensors that can continuously monitor various aspects of human health [1]. Wearable sensors have the potential to revolutionize healthcare by enabling real-time, non-invasive, and long-term monitoring of physiological and biochemical parameters [2]. These sensors can be integrated into various wearable devices, such as smartwatches, fitness bands, patches, and clothing, making them easily accessible and convenient for users [3]. The data collected by wearable sensors can provide valuable insights into an individual's health status, allowing for early detection of abnormalities, timely intervention, and personalized treatment. One of the key advantages of wearable sensors is their ability to monitor health parameters continuously, outside of clinical settings. This is particularly important for managing chronic conditions, such as diabetes [4], cardiovascular diseases [5], and respiratory disorders [6], which require regular monitoring

and management. By tracking relevant biomarkers and vital signs, wearable sensors can alert users and healthcare providers to potential health issues before they escalate, enabling proactive care and reducing the risk of complications. Moreover, wearable sensors can facilitate remote monitoring of patients, reducing the need for frequent hospital visits and improving the quality of life for individuals with chronic conditions.

Wearable sensors also play a crucial role in preventive healthcare by empowering individuals to take control of their health and well-being [7–11] (Figure 1). The data collected by these sensors can provide users with personalized insights into their daily activities [12], sleep patterns [13], stress levels [14], and other lifestyle factors that influence health. This information can motivate users to adopt healthier behaviors, such as increasing physical activity, improving sleep hygiene, and managing stress. Furthermore, the integration of wearable sensors with mobile health (mHealth) applications and digital health platforms can provide users with personalized recommendations, coaching, and support to help them achieve their health goals [15].



**Figure 1.** A schematic of different parts of the body that can be used for health sensing monitoring.

Among the various techniques used for fabricating wearable sensors, LbL self-assembly has emerged as a powerful and versatile approach. LbL self-assembly is a bottom-up nanofabrication technique that involves the alternating deposition of oppositely charged materials, such as polymers, nanoparticles, or biomolecules, onto a substrate [16]. The LbL process exploits the electrostatic interactions, hydrogen bonding, or other intermolecular forces between the deposited layers to create stable and uniform multilayered films [17]. The thickness, composition, and structure of the LbL films can be precisely controlled by adjusting the deposition conditions, such as the number of layers, pH, ionic strength, and temperature [18]. One of the key advantages of the LbL technique is its ability to create conformal and flexible films on various substrates, including planar surfaces, fibers, and three-dimensional structures [19]. This makes LbL self-assembly particularly suitable for fabricating wearable sensors that can conform to the curved surfaces of the human body and withstand the mechanical stresses associated with daily wear. Moreover, the LbL technique enables the incorporation of multiple functional materials within the same film, allowing for the development of multi-functional sensors that can simultaneously detect various analytes or stimuli [20].

Another advantage of LbL self-assembly is its simplicity and cost-effectiveness compared to other nanofabrication techniques, such as photolithography and chemical vapor deposition. The LbL process can be carried out under ambient conditions using aqueous solutions, eliminating the need for expensive equipment and harsh chemicals [21,22]. Furthermore, the LbL technique is highly scalable and can be easily adapted for large-scale manufacturing, making it attractive for commercial applications. The nanoscale control over the film architecture afforded by the LbL technique also enables the fabrication of highly sensitive and selective sensors. By tuning the composition and structure of the LbL films, it is possible to create sensors with enhanced surface area, porosity, and molecular recognition capabilities. For example, the incorporation of nanoparticles or nanoporous materials within the LbL films can increase the surface area available for analyte binding, leading to improved sensitivity [23]. Similarly, the use of molecularly imprinted polymers or aptamers as recognition elements can impart high selectivity towards specific target analytes [24].

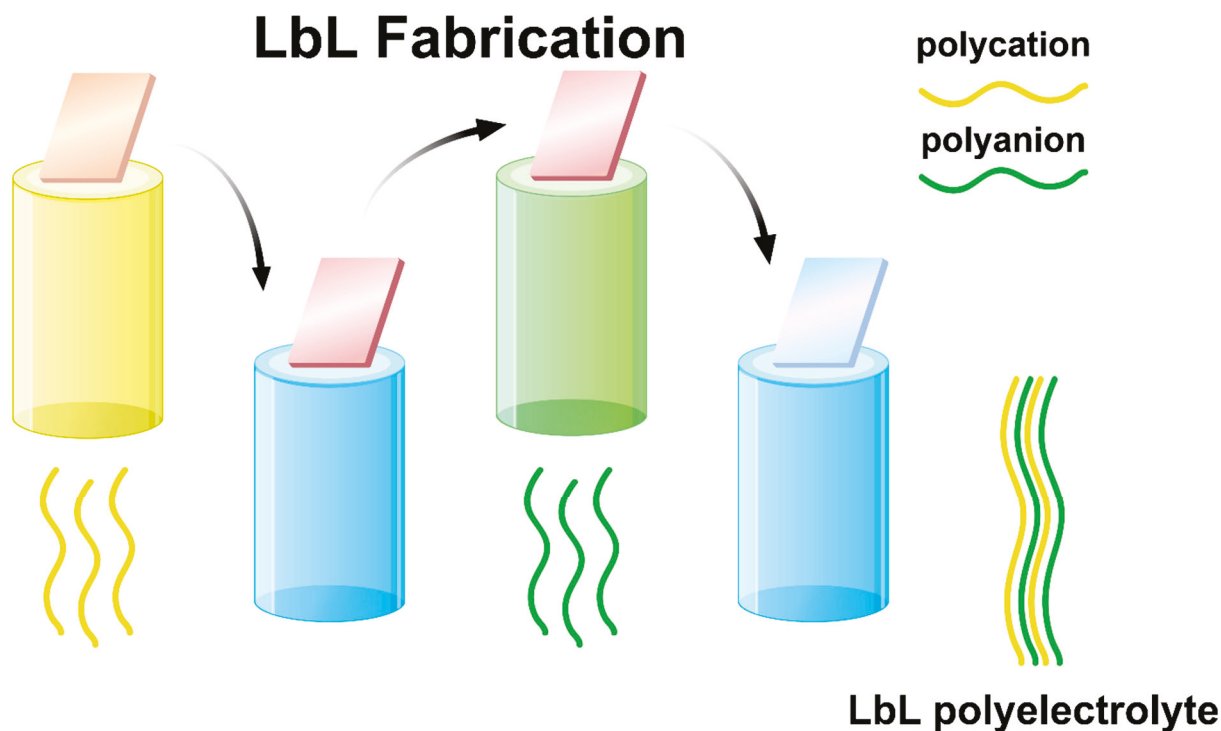
Polymers are the backbone of LbL self-assembly and play a crucial role in the fabrication of wearable sensors. Polymers serve as the building blocks for creating the multilayered films that form the basis of the sensor. They provide the necessary functional groups for electrostatic interactions, hydrogen bonding, or other intermolecular forces that drive the LbL assembly process. Moreover, polymers offer a wide range of properties, such as mechanical strength, flexibility, biocompatibility, and stimuli-responsiveness, which can be tailored to meet the specific requirements of the sensor application. This review aims to provide a comprehensive overview of the recent advancements in polymer-assisted LbL fabrication of wearable sensors for health monitoring. The review begins by introducing the principles of LbL self-assembly, including the fundamental mechanisms of film growth, the factors affecting the film properties, and the characterization techniques used to study LbL films [25]. The role of polymers in LbL sensor fabrication is then discussed in detail, highlighting the unique properties and functionalities of natural and synthetic polymers. The review then delves into the various types of wearable sensors that can be fabricated using the LbL technique, categorized based on their sensing mechanisms. The potential applications of LbL-fabricated wearable sensors in various domains of health monitoring are then discussed. The use of wearable sensors for disease diagnosis is also explored. Finally, the review discusses the challenges and future perspectives in the field of polymer-assisted LbL fabrication of wearable sensors.

## 2. Principles of LbL Self-Assembly

### 2.1. Fundamentals of LbL Film Growth

The LbL self-assembly technique is based on the alternating deposition of oppositely charged materials onto a substrate, resulting in the formation of multi-layered thin films. The most common driving force for LbL film growth is electrostatic interaction between the positively and negatively charged components (Figure 2) [26]. The LbL process typically involves the following steps: (1) immersion of the substrate into a solution containing a positively charged material, (2) rinsing to remove loosely bound material, (3) immersion into a solution containing a negatively charged material, and (4) rinsing again. This cycle is repeated until the desired number of layers or film thickness is achieved.

The growth of LbL films is influenced by several factors, including the charge density of the deposited materials, the ionic strength of the solutions, the pH, and the temperature. The charge density of the materials determines the amount of material deposited in each layer and the stability of the resulting film [17]. Higher charge densities generally lead to thicker films and stronger electrostatic interactions between the layers. The ionic strength of the solutions affects the conformation of the deposited materials and the screening of the charges [27]. At low ionic strengths, the materials adopt a more extended conformation due to the reduced screening of the charges, resulting in thicker films. Conversely, at high ionic strengths, the materials adopt a more coiled conformation, leading to thinner films [20].



**Figure 2.** A schematic illustration of the alternate adsorption of the polyelectrolyte species to produce a multi-layered structure.

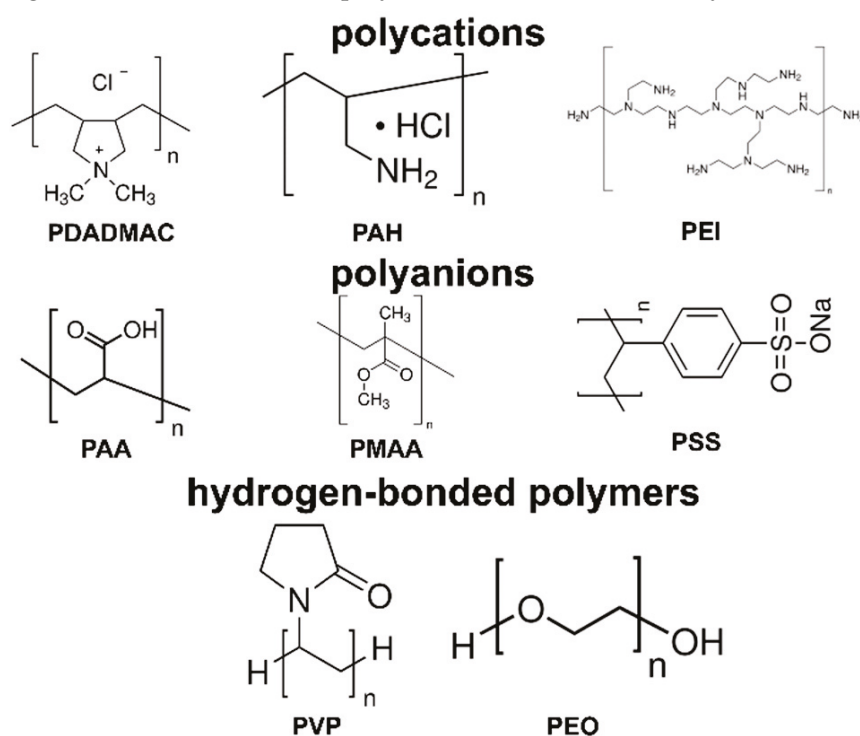
The pH of the solutions can also have a significant impact on the growth of LbL films, particularly when weak polyelectrolytes, such as polyacrylic acid (PAA) and polyallylamine hydrochloride (PAH), are used. The degree of ionization of weak polyelectrolytes is dependent on the pH, which in turn affects their charge density and the strength of the electrostatic interactions [28]. For example, PAA is more ionized at high pH values, while PAH is more ionized at low pH values. By adjusting the pH of the solutions, it is possible to control the thickness and the composition of the LbL films [29]. Temperature is another parameter that can influence the growth of LbL films [30]. Higher temperatures can lead to increased diffusion of the deposited materials and reorganization of the film structure. This can result in smoother and more homogeneous films. However, high temperatures can also cause denaturation of sensitive materials, such as proteins and enzymes, which can compromise their functionality [31,32].

The growth behavior of LbL films can be monitored using various techniques, such as quartz crystal microbalance with dissipation (QCM-D) [33,34], ellipsometry [35], and surface plasmon resonance (SPR) [36]. QCM-D measures the mass and viscoelastic properties of the films in real-time, providing information on the thickness and the conformation of the deposited layers. Ellipsometry measures the change in polarization of light upon reflection from the film surface, allowing for the determination of the film thickness and refractive index. SPR measures the change in the refractive index of the film surface, which is related to the mass of the deposited material.

## 2.2. Polymer-Assisted LbL Assembly

Polymers play a crucial role in the LbL self-assembly process, serving as the building blocks for the multi-layered films. The most commonly used polymers in LbL assembly are polyelectrolytes, which are polymers with ionizable groups that can dissociate in aqueous solutions, giving rise to positively or negatively charged chains. Examples of positively charged polyelectrolytes (polycations) include poly(diallyldimethylammonium chloride) (PDADMAC) [37], PAH [29], and polyethyleneimine (PEI) [38]. Examples of negatively charged polyelectrolytes (polyanions) include poly(styrene sulfonate) (PSS) [39], PAA [29],

and poly(methacrylic acid) (PMAA) [40]. The use of polyelectrolytes in LbL assembly offers several advantages. First, polyelectrolytes have a high charge density, which enables the formation of stable and uniform multi-layers through strong electrostatic interactions. Second, polyelectrolytes are water-soluble, which allows for the LbL process to be carried out under mild and environmentally friendly conditions. Third, polyelectrolytes can be easily functionalized with various chemical groups, such as carboxylic acids, amines, and thiols, which can be used to impart specific properties or to covalently attach other molecules, such as dyes, drugs, or biomolecules [41,42]. In addition to polyelectrolytes, other types of polymers have also been used in LbL assembly. For example, hydrogen-bonded polymers, such as poly(vinylpyrrolidone) (PVP) [43] and poly(ethylene oxide) (PEO) [44], can be assembled through hydrogen bonding interactions. These polymers are often used in combination with polyelectrolytes to create more complex and functional multi-layers. Another example is the use of block copolymers, which consist of two or more chemically distinct polymer segments covalently bonded together. Block copolymers can self-assemble into various nanostructures, such as micelles, vesicles, and cylinders [45,46], which can be exploited in LbL assembly to create hierarchical and stimuli-responsive films. Figure 3 shows the common polymers used for LbL assembly.



**Figure 3.** Common polymers used for LbL assembly.

Polymer-assisted LbL assembly has been widely used in the fabrication of wearable sensors. For example, Wu et al. [47] focused on developing a highly sensitive and stretchable strain sensor for monitoring tiny motions. By using a layer-by-layer approach, an ultrathin conductive layer was applied to a polyurethane yarn. This method significantly improved the sensor's sensitivity, with a gauge factor of 201, and its stretchability, reaching up to 100% strain. The sensor also proved to be wash-durable, maintaining its performance even after multiple wash cycles. Polymer-assisted LbL assembly has also been used to create wearable biosensors. For instance, Lee et al. [48] constructed an electrochemical biosensors through a hydrodynamic LbL assembly technique. This method focused on creating enzymatic conductive nano-networks, which were pivotal for the enzyme-sticker-based contact printing of these sensors. The findings revealed that biosensors developed using this technique exhibited remarkable improvements, particularly in sensitivity and stability. For instance, glucose and lactate biosensors fabricated through this method demonstrated



exceptional sensitivity and rapid response times, alongside prolonged operational stability. These advancements underscore the effectiveness of the LbL assembly in optimizing biosensor technology, suggesting a significant leap forward in the field of electrochemical detection and analysis.

### 2.3. Factors Affecting LbL Film Properties

The properties of LbL films, such as thickness, roughness, porosity, and mechanical strength, are influenced by various factors, including the type and concentration of the materials, the pH and ionic strength of the solutions, the deposition time and temperature, and the post-treatment conditions. Understanding and controlling these factors is crucial for optimizing the performance of LbL-based wearable sensors. The type and concentration of the materials used in LbL assembly have a significant impact on the properties of the resulting films. For example, the use of high-molecular-weight polymers or nanoparticles with a high aspect ratio can lead to thicker and rougher films [49], while the use of low-molecular-weight polymers or spherical nanoparticles can result in thinner and smoother films [50]. The concentration of the materials in the deposition solutions also affects the thickness and the growth rate of the films, with higher concentrations generally leading to thicker films and faster growth rates [51].

The pH and ionic strength of the deposition solutions can also influence the properties of the LbL films. The pH affects the charge density and the conformation of the materials, particularly for weak polyelectrolytes or pH-sensitive materials (described in Section 2.1). The deposition time and temperature are other important factors that can affect the properties of the LbL films. Longer deposition times generally result in thicker films, but can also lead to the diffusion and reorganization of the layers, particularly for materials with high mobility. In a comprehensive study by Yang et al. [52], the effect of deposition time on the growth characteristics of clay-based thin films was meticulously analyzed. Conducting their research through a LbL assembly technique, they discovered a direct correlation between deposition time and the thickness of the films (Figure 4). Specifically, longer deposition times led to significantly thicker films, with the growth rate of these films showing a marked increase. This thickness was not just about size; it also influenced the films' density and uniformity, improving with extended deposition times. The study highlighted that by manipulating the deposition time, one could effectively control the physical properties of the thin films, such as their thickness, density, and uniformity. Higher temperatures can also promote the diffusion and reorganization of the layers, but can also cause the denaturation or degradation of sensitive materials, such as proteins or enzymes. Chang et al. [53] explored the construction of multi-layer films using poly(*N*-acryloyl-*N*'-propylpiperazine) (PACrNPP) and PAA through a LbL assembly technique. Their investigation focused on how temperature influenced the assembly process. It was discovered that below the lower critical solution temperature (LCST) of PACrNPP, which is around 37 °C, the amount of polymer adsorbed onto the films increased as the temperature rose. This trend was attributed to a change in the conformation of PACrNPP polymers at different temperatures. Specifically, at temperatures approaching its LCST, PACrNPP tends to adopt a more compact conformation, leading to increased adsorption.

Post-treatment conditions, such as drying, annealing, or crosslinking, can also have a significant impact on the properties of the LbL films. Drying the films can cause shrinkage and collapse of the layers, particularly for highly porous or hydrated films [54]. Annealing the films at elevated temperatures can improve the mechanical properties and the stability of the films, but can also cause the loss of sensitive materials or the formation of cracks or defects [55]. Crosslinking the films with chemical agents, such as glutaraldehyde or carbodiimide [56,57], can enhance the mechanical strength and the resistance to dissolution or swelling of the films, but can also reduce the flexibility or the responsiveness of the films.

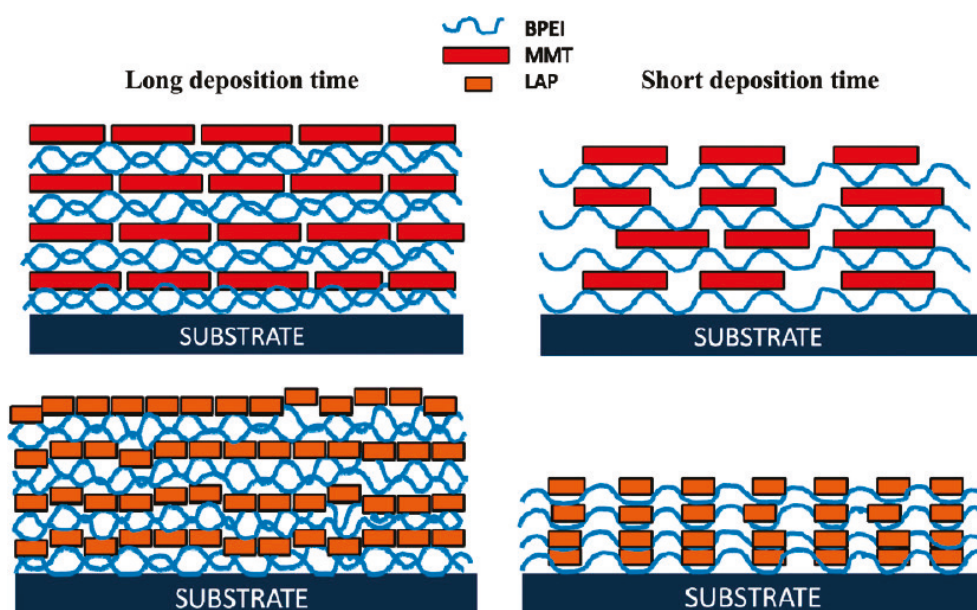


Figure 4. Film growth mechanism for BPEI/MMT and BPEI/LAP with different deposition times [52].

### 3. Polymers Used in LbL Sensor Fabrication

#### 3.1. Natural Polymers

Natural polymers have gained significant attention in the field of LbL sensor fabrication due to their unique properties, such as biocompatibility, biodegradability, and renewability. These polymers are derived from natural sources, such as plants, animals, or microorganisms, and offer several advantages over synthetic polymers, including low toxicity, low immunogenicity, and the ability to mimic the natural extracellular matrix [58]. In this section, we will discuss the use of various natural polymers, including cellulose nanofibers/nanocrystals, chitosan (CS), and other biopolymers, in the fabrication of LbL-based sensors.

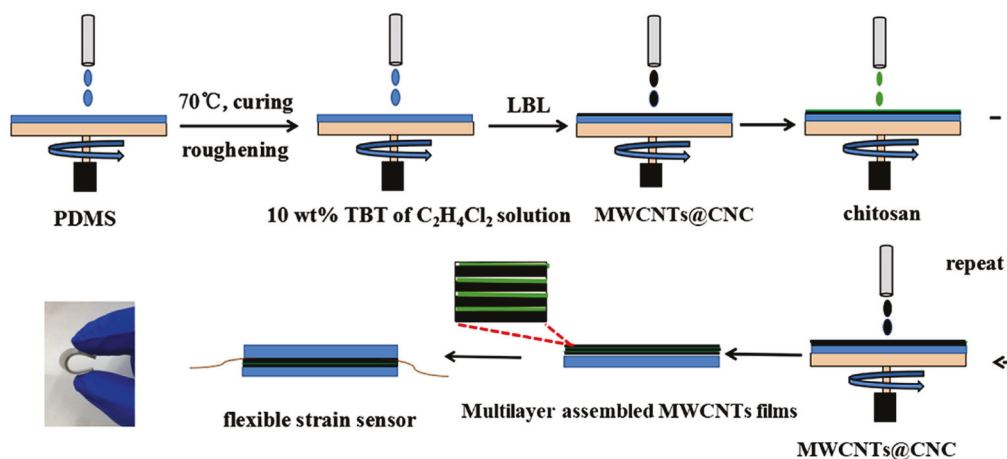
##### 3.1.1. Cellulose Nanofibers/Nanocrystals

Nanocelluloses, including cellulose nanofibers (CNFs) and cellulose nanocrystals (CNCs), have emerged as promising building blocks for LbL assembly due to their unique properties, such as high mechanical strength, large surface area, and excellent biocompatibility [59,60]. CNFs are long, flexible, and entangled fibers with diameters in the range of 5–100 nm and lengths of several micrometers. CNCs, on the other hand, are short, rod-like, and highly crystalline particles with diameters of 5–20 nm and lengths of 100–500 nm. The use of nanocelluloses in LbL assembly offers several advantages over synthetic polymers [61–63]. First, nanocelluloses are renewable, biodegradable, and non-toxic, making them environmentally friendly and sustainable materials for wearable sensors. Second, nanocelluloses have a high density of surface hydroxyl groups, which can be easily modified with various functional groups, such as carboxylic acids, amines, and sulfates, to impart specific properties or to enable LbL assembly. Third, nanocelluloses have a high aspect ratio and a large surface area, which can enhance the sensitivity and the response time of the sensors.

LbL assembly using nanocelluloses typically involves the alternating deposition of positively and negatively charged nanocelluloses or the combination of nanocelluloses with other charged materials, such as polyelectrolytes or nanoparticles. For example, Mougo et al. [64] developed a wearable sensor designed to monitor cortisol levels in human sweat, utilizing a novel approach that leverages the properties of CNC. The incorporation of CNC played a pivotal role in enhancing the sensor's performance, primarily due to CNC's ability to increase the surface area for the conductive layers and improve the sensor's sensitivity and stability. This was evident in the sensor's rapid response to cortisol detection, with

a notably high sensitivity that could accurately measure physiological cortisol levels in sweat. Through meticulous testing, including the analysis of sweat samples collected from individuals after exercise, the sensor showed its capability to provide reliable and precise measurements of cortisol levels, showcasing its potential as a non-invasive tool for monitoring stress and health conditions in real-time.

In another example, Chen et al. [65] developed an innovative strain sensor by employing a multi-layer LbL assembly technique, utilizing CNC and CS as the primary materials. This bioinspired approach led to the creation of a nanocomposite with a unique microcrack architecture, significantly enhancing the sensor's sensitivity to strain (Figure 5). The incorporation of CNC into the matrix allowed for a better dispersion of multi-walled carbon nanotubes (MWCNTs), which are crucial for the sensor's conductivity. The CS, on the other hand, acted as a binder that improved the adhesion between the MWCNTs and the polymer base, contributing to the overall durability and flexibility of the sensor. The resulting nanocomposite exhibited an ultrahigh gauge factor of approximately 359 and a detection limit as low as 0.5%, showcasing its ability to accurately detect even minute strains. This high performance was further demonstrated through various tests, including monitoring of finger movements, swallowing, coughing, deep breathing, and facial expressions, indicating its potential applicability in areas such as wearable electronics and healthcare monitoring.



**Figure 5.** Schematic illustration of the fabrication of the multi-layer assembled MWCNTs@CNC-PDMS nanocomposites and photograph of the strain sensor being folded [65].

LbL assembly using nanocelluloses has also been used to create multi-functional sensors. For instance, Mugo et al. [66] reported a wearable sensor capable of simultaneously monitoring pH and cortisol levels in sweat, leveraging the unique properties of CNC and a dual detection approach. Fabricated using a LbL technique, the sensor integrated a pH-responsive polyaniline (PANI) layer and a cortisol-sensing layer made from a molecularly imprinted polymer (MIP), both printed onto a conductive microneedle substrate. The utilization of CNC in the sensor design was pivotal for enhancing the mechanical strength and flexibility of the microneedles, ensuring durability and comfort for wearers. The sensor's performance demonstrated a linear response to pH within the physiologically relevant range of 3.0–9.3, with a calibration sensitivity of 4.7  $\mu\text{F}/\text{pH}$  at room temperature. The cortisol sensor, leveraging the selectivity of MIP towards cortisol, exhibited a linear detection range up to 66 ng/mL.

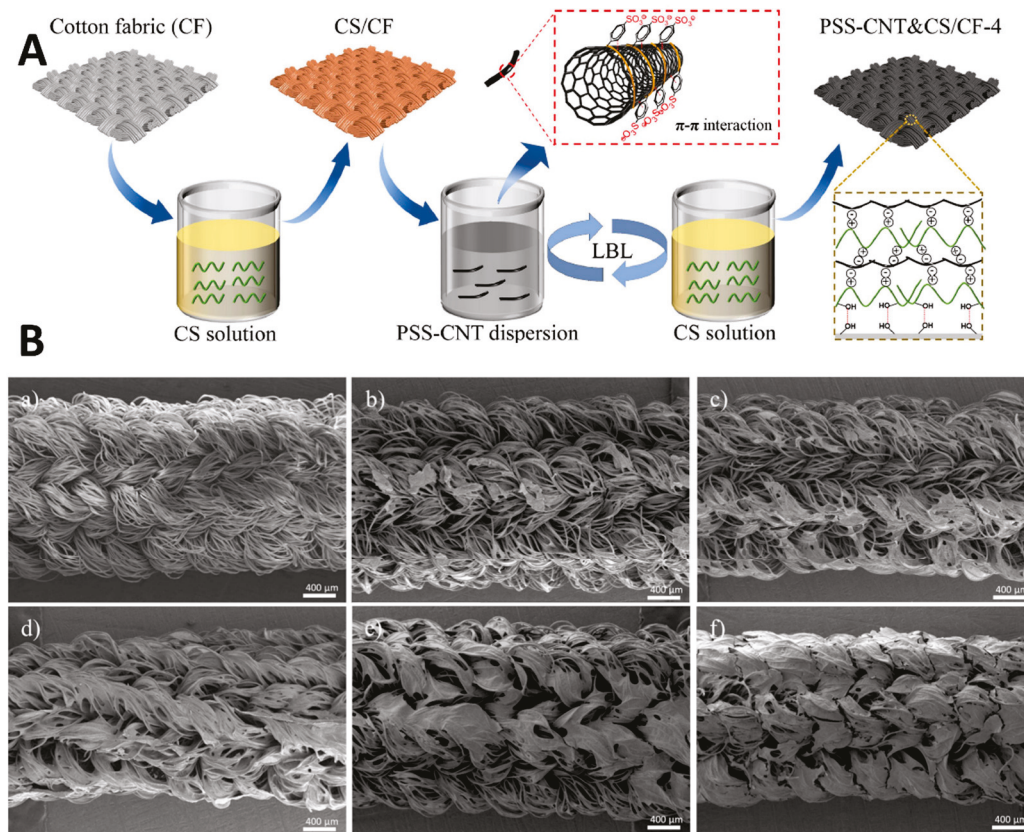
### 3.1.2. Chitosan (CS)

CS is a linear polysaccharide composed of randomly distributed  $\beta$ -(1 $\rightarrow$ 4)-linked D-glucosamine and N-acetyl-D-glucosamine units. It is obtained by the deacetylation of chitin, which is the second most abundant biopolymer after cellulose and is found in the exoskeletons of crustaceans and insects. CS has several unique properties that make it attractive for LbL sensor fabrication, including its biocompatibility, biodegradability, and antimicrobial activity [67]. CS is a cationic polymer due to the presence of primary amine groups on its backbone, which can be protonated in acidic solutions. This property enables the LbL assembly of chitosan with anionic polymers or nanoparticles through electrostatic interactions [68]. CS can also form hydrogen bonds and hydrophobic interactions with other materials, which can further stabilize the LbL films [69].

Several studies have demonstrated the use of chitosan in the fabrication of LbL-based sensors. For example, Zhang et al. [70] developed an environmentally friendly method for creating flexible conductive cotton fabric (FCCF) by employing a LbL assembly technique that avoids the chemical modification of CNTs. This method involved alternately dipping cotton fabric into CS and CNTs solutions, resulting in a material that combines the benefits of both components (Figure 6A). The fabricated FCCF demonstrated impressive mechanical stability, maintaining its electrical resistivity even after 500 cycles of mechanical abrasion and tape peeling. Its electrical conductivity reached over 30 S/m after applying four layers of CNTs, showcasing its potential for wearable sensor applications. The FCCF exhibited remarkable strain sensing capabilities, with a gauge factor as high as 35.1 and a quick response time of 70 ms, making it adept at monitoring various human movements like finger bending and joint activities. Additionally, it proved to be an effective temperature sensor within the range of 30–100 °C, displaying stable and reproducible negative temperature sensing behavior. Li et al. [71] developed a humidity sensor by creating ultrathin multi-layers of MXene/CS-quercetin. This sensor demonstrated exceptional performance in detecting humidity changes, attributed to the unique assembly method inspired by the layered structure of onions. By alternating layers of  $\text{Ti}_3\text{C}_2\text{T}_x$  MXene with CS-quercetin, the team enhanced the material's response to water molecules, achieving a remarkable sensitivity increase. Specifically, the sensor showed a 317% response at 90% relative humidity, alongside an ultrafast response time of 0.75 s, and maintained its stability for over 15 days. The purposeful inclusion of CS in the multi-layer structure not only improved water molecule adsorption due to its hydrophilic nature but also contributed to the sensor's overall stability by preventing MXene degradation.

In another study, Kong et al. [72] developed a novel fiber-shaped temperature sensor by employing a LbL self-assembly technique, which meticulously coated polyurethane fibers with reduced graphene oxide (rGO) and CS (Figure 6B). The inclusion of CS played a pivotal role, not only enhancing the sensor's temperature sensitivity but also its mechanical stability. The sensor showcased remarkable performance metrics, including an impressive stretchability of up to 80%, a high temperature sensitivity of  $-1.379\%$  per degree, and ultrafast response and recovery times of 2.4 and 3.9 s, respectively. These attributes underscore the sensor's potential for real-time temperature monitoring in wearable applications. The study's findings highlight the synergistic effects of combining rGO and CS through the LbL method, resulting in a sensor that offers both high sensitivity and rapid responsiveness to temperature changes, making it an ideal candidate for integration into wearable healthcare devices.





**Figure 6.** (A) LBL assembly of CS and PSS-CNT on CF to fabricate the FCCF [70]. (B) SEM images of (a) control fiber, (b) (rGO)<sub>6</sub>@PF, (c) (rGO@CS)<sub>1</sub>@PF, (d) (rGO@CS)<sub>6</sub>@PF, (e) (rGO@CS<sub>1</sub>)<sub>6</sub>@PF, (f) (rGO@CS<sub>3</sub>)<sub>6</sub>@PF [72].

### 3.1.3. Other Biopolymers

In addition to cellulose and chitosan, several other biopolymers have been used in the fabrication of LbL-based sensors, including alginate [73], gelatin [74], and silk fibroin (SF) [75]. These biopolymers offer unique properties and functionalities that can be exploited for various sensing applications.

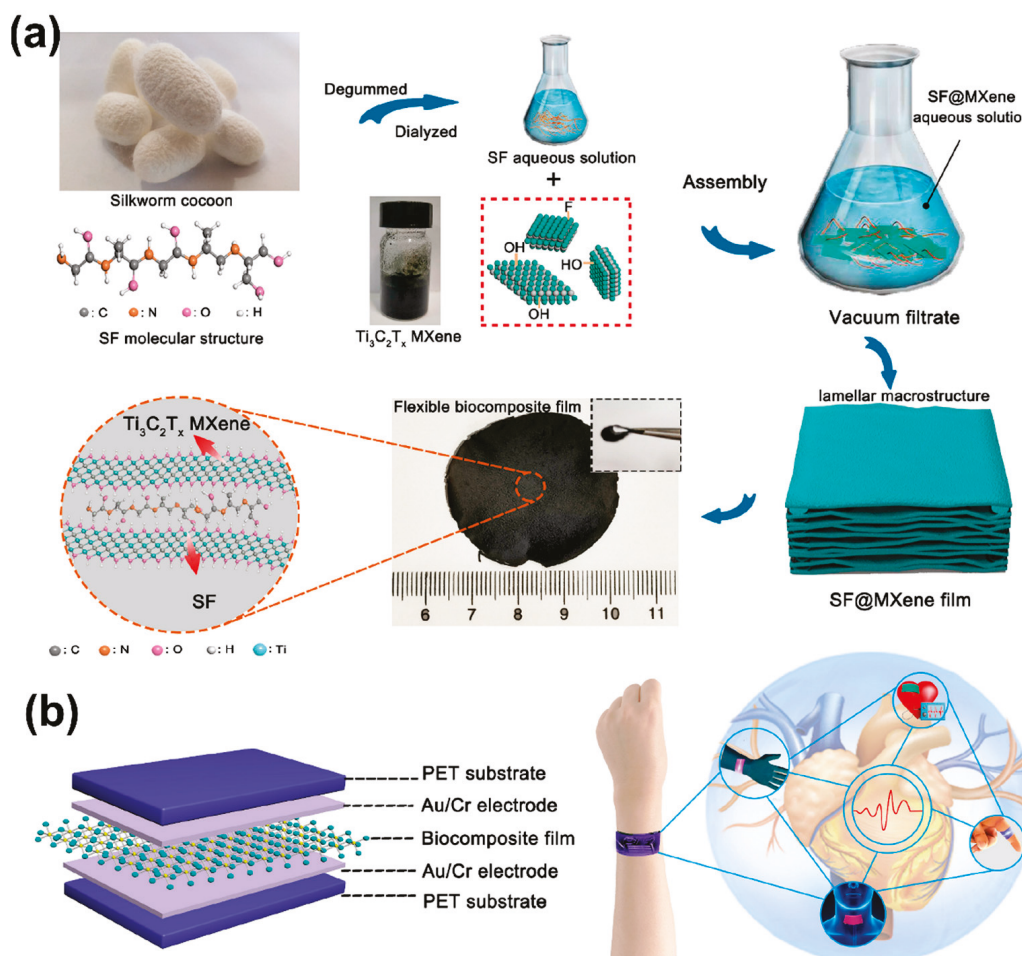
Alginate is a linear polysaccharide composed of  $\beta$ -D-mannuronic acid and  $\alpha$ -L-guluronic acid units, which is obtained from brown algae. Alginate is an anionic polymer due to the presence of carboxylic acid groups on its backbone, which can form electrostatic interactions with cationic polymers or nanoparticles. For example, Wang et al. [76] developed a flexible wearable temperature sensor crafted from a graphene/alginate composite non-woven fabric. This sensor demonstrated exceptional performance, characterized by its high sensitivity, accuracy, and stability, which are crucial for the continuous and stable monitoring of skin temperature. The use of sodium alginate played a pivotal role in the sensor's fabrication process, serving as an effective dispersant for graphene, thereby enhancing the material's overall homogeneity and flexibility. The sensor's capability to accurately detect subtle temperature changes on the skin surface was particularly noteworthy. It exhibited a remarkable sensitivity with a temperature coefficient of resistance (TCR) value of  $-1.5\text{ }^{\circ}\text{C}^{-1}$ , ensuring high accuracy up to  $0.1\text{ }^{\circ}\text{C}$ , and boasted a rapid response time of 26.3 s within the  $20\text{--}37\text{ }^{\circ}\text{C}$  range.

Gelatin is a protein derived from the hydrolysis of collagen, which is the main component of connective tissues in animals. Gelatin is a biocompatible and biodegradable polymer that can form LbL films through hydrogen bonding and hydrophobic interactions. Li et al. [74] developed tactile sensors based on gelatin methacryloyl (GelMA) for use in medical wearables, focusing on their application, fabrication, and performance. GelMA was chosen for its biocompatibility and tunable mechanical properties, making it ideal for



wearable sensors that require flexibility and durability. The study showcased the sensors' ability to accurately measure and respond to pressure, stretch, and other mechanical forces, which are essential qualities for monitoring patient health in real-time. Specifically, the sensors demonstrated a remarkable sensitivity to pressure changes, with a detection limit as low as 0.1 kPa and a fast response time, enhancing their utility in wearable devices. By integrating these GelMA-based sensors into medical wearables, the study aimed to improve patient care through continuous, non-invasive monitoring of vital signs and physical states.

SF is a protein obtained from the cocoons of silkworms, which has a unique combination of mechanical strength, flexibility, and biocompatibility. SF can form LbL films through hydrogen bonding and hydrophobic interactions. In a recent study [77], researchers crafted a SF@MXene biocomposite film by ingeniously integrating SF with MXene nanosheets, leveraging SF's natural properties as a bridging agent (Figure 7). This innovative approach resulted in a film characterized by a unique wave-shaped lamellar macrostructure, which significantly enhanced its flexibility and mechanical durability. The film showcased an impressive low elastic modulus of 1.22 MPa, high sensitivity of  $25.5 \text{ kPa}^{-1}$ , a remarkably low detection limit of 9.8 Pa, and sustained its performance over 3500 cycles, indicating its robustness. A pivotal aspect of this study was the film's ability to detect subtle human physiological movements such as phonations and wrist pulses with high precision, demonstrating its potential as a versatile tool for monitoring human health. Furthermore, the biocompatibility of the SF@MXene film was rigorously tested, revealing its safety for integration with human skin, as evidenced by the viability of human skin fibroblast-HSAS1 cells.



**Figure 7.** (a) Illustration of preparation of the SF@MXene biocomposite film and flexible pressure sensor. (b) Schematic illustration of SF@MXene biocomposite film-based flexible pressure sensor and its application in human health detection [77].

### 3.2. Synthetic Polymers

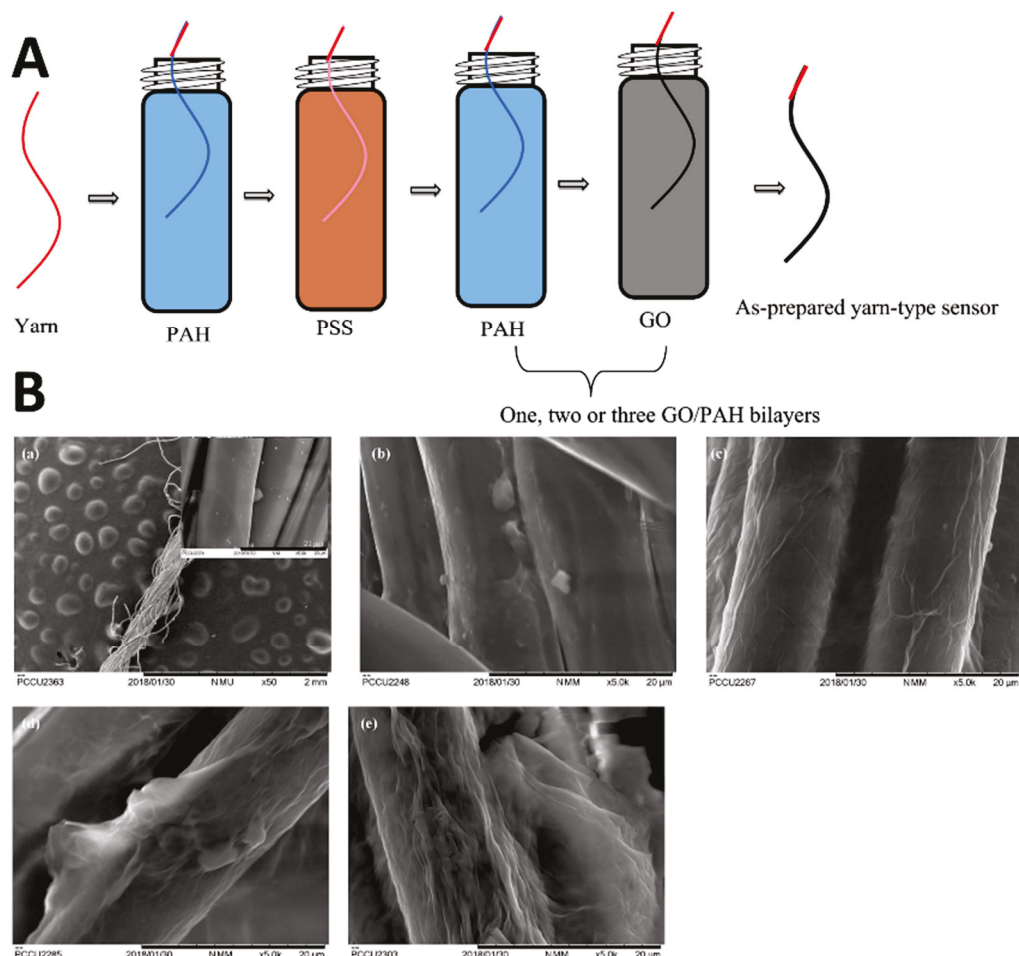
Synthetic polymers have been widely used in the fabrication of LbL-based sensors due to their versatility, stability, and tunability. These polymers are artificially synthesized from monomers and can be designed with specific functional groups, molecular weights, and architectures to meet the requirements of various sensing applications. In this section, we will discuss the use of various synthetic polymers, including polyelectrolytes, conductive polymers, and stimuli-responsive polymers, in the fabrication of LbL-based sensors.

#### 3.2.1. Polyelectrolytes

Polyelectrolytes are polymers that contain ionizable groups, such as carboxylic acids, sulfonic acids, or amines, which can dissociate in aqueous solutions to form charged chains. Polyelectrolytes can be classified as strong or weak, depending on the degree of dissociation of their ionizable groups. Strong polyelectrolytes, such as PSS and PDADMAC, are fully charged over a wide range of pH values, while weak polyelectrolytes, such as PAA and PAH, are partially charged and their degree of ionization depends on the pH of the solution. Polyelectrolytes are the most commonly used building blocks for LbL assembly due to their ability to form stable and uniform films through electrostatic interactions [78]. The LbL assembly of polyelectrolytes is typically performed by alternately exposing a substrate to solutions of polycations and polyanions, with a rinsing step in between to remove loosely bound chains [79]. The thickness and the properties of the resulting films can be controlled by adjusting various parameters, such as the pH, ionic strength, and temperature of the solutions, as well as the number of deposition cycles.

Several studies have demonstrated the use of polyelectrolytes in the fabrication of LbL-based sensors. For example, Su and Liao [80] developed a flexible textile-type  $\text{NH}_3$  gas sensor by employing a LbL self-assembly technique to deposit GO on a single yarn substrate. The process began with the creation of a precursor layer through the deposition of PSS/PAH bilayer on the yarn. This was followed by the LBL assembly of GO/PAH monolayers and multi-layers  $(\text{GO}/\text{PAH})_n$ , where  $n$  indicates the number of layers (Figure 8A), enhancing the sensor's structure. The incorporation of PAH played a crucial role in achieving a stable layering of GO, which was critical for the sensor's performance. SEM was utilized to analyze the thin films' microstructure, revealing the successful layering (Figure 8B). The study's primary findings highlighted the sensor's exceptional sensitivity to  $\text{NH}_3$  gas at room temperature, attributing this capability to the efficient ion transport within the  $(\text{GO}/\text{PAH})_n/\text{PSS}/\text{PAH}$  thin films. This ion transport mechanism significantly increased the conductivity of the films in the presence of  $\text{NH}_3$  gas, thereby improving the sensor's performance. Among the configurations tested, the sensor comprising a single  $(\text{GO}/\text{PAH})_1$  thin film exhibited the highest sensitivity, demonstrating excellent linearity, rapid response and recovery times, and notable selectivity towards  $\text{NH}_3$ .

In another study, Bai et al. [81] explored the sensors demonstrated remarkable self-healing capabilities at room temperature, transparency, and flexibility. Specifically, the incorporation of PAA within the LbL structures played a crucial role in achieving efficient self-healing properties without compromising the sensor's performance. The study showed that these sensors could recover their initial conductivity effectively after being cut, with a healing efficiency reaching up to 90% under ambient conditions. This self-healing process was facilitated by hydrogen bonding in the PAA layers, which allowed the sensors to maintain their structural integrity and functionality after damage. Additionally, the application of these sensors in wearable technology was highlighted, showing potential for real-time monitoring of various physical activities through seamless integration with human skin or clothing.



**Figure 8.** (A) Schematic diagram of GO multi-layer thin films assembled on a single yarn. (B) SEM images of (a) bare yarn (inset: enlarged image), (b) (PSS/PAH)/yarn, (c) (GO/PAH)<sub>1</sub>(PSS/PAH)/yarn, (d) (GO/PAH)<sub>2</sub>(PSS/PAH)/yarn and (e) (GO/PAH)<sub>3</sub>(PSS/PAH)/yarn [80].

### 3.2.2. Conductive Polymers

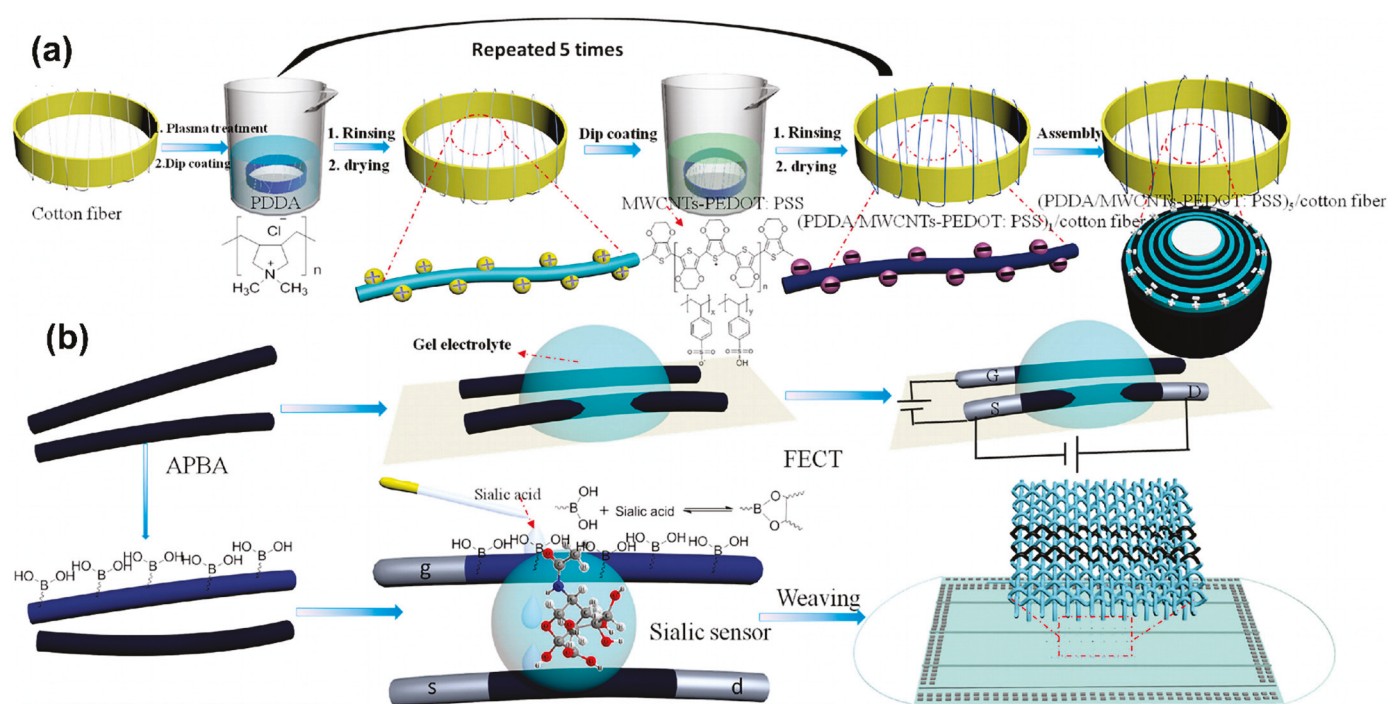
Conductive polymers are a class of polymers that can conduct electricity due to the presence of conjugated double bonds in their backbone. These polymers have gained significant attention in the field of sensor fabrication due to their unique combination of electrical conductivity, optical properties, and processability. The most commonly used conductive polymers for LbL assembly include PANI, polypyrrole (PPy), and poly(3,4-ethylenedioxythiophene) (PEDOT). Conductive polymers can be deposited onto a substrate through various methods, such as electropolymerization [82], chemical oxidation [83], or vapor deposition [84]. However, the LbL assembly of conductive polymers offers several advantages, such as the ability to control the thickness and the morphology of the films, the possibility of incorporating other functional materials, such as nanoparticles or biomolecules, and the compatibility with flexible and stretchable substrates.

Several studies have demonstrated the use of conductive polymers in the fabrication of LbL-based sensors. For example, Gunasekara et al. [85] developed a smart wearable pressure sensor by fabricating a composite of MWNTs and Ppy on an aerogel substrate. This innovative approach aimed to enhance the sensor's sensitivity and conductivity for effective human body movement detection. Initially, the aerogel was coated with MWNTs to create a conductive network, followed by the addition of Ppy through in situ polymerization. This method not only improved the composite's electrical properties but also its sensitivity to pressure changes. The application of polydopamine (PDA) as a substrate surface modification technique further augmented these effects, contributing to



the sensor's impressive performance. With a sensitivity of  $34.64 \text{ kPa}^{-1}$  at a low pressure of 1 kPa, the sensor demonstrated high sensitivity, acceptable conductivity, and remarkable stability over 5000 continuous pressure cycles in the pressure range of 0.45–4 kPa. Its lowest detection level was approximately 0.2 kPa, indicating its potential for detecting subtle human movements. The study highlighted the significant role of PPy in enhancing the sensor's performance, particularly in terms of sensitivity and stability. The LbL assembly technique used in the sensor's fabrication played a crucial role in achieving these results.

In another study, Zhu et al. [86] developed a composite conductive fiber, leveraging the LbL assembly technique. This fiber was integral to the creation of fiber-based organic electrochemical transistors (FECTs), which were then applied in the sensitive detection of sialic acid (SA), showcasing their potential for wearable sensor applications (Figure 9). The core of this innovation was the utilization of PEDOT, combined with the LbL method, to fabricate the conductive fibers that formed the basis of the FECTs. These FECTs demonstrated exceptional performance metrics, including high sensitivity and stability, which are crucial for real-world applications. Specifically, the FECTs were modified with 3-aminophenylboronic acid to create a biosensor capable of recognizing SA with remarkable sensitivity, indicating a significant advancement in the field of wearable biosensors.



**Figure 9.** (a) Schematic diagram of LbL assembly of composite conductive fiber. (b) Preparation of FECT and FECT based sialic acid sensor [86].

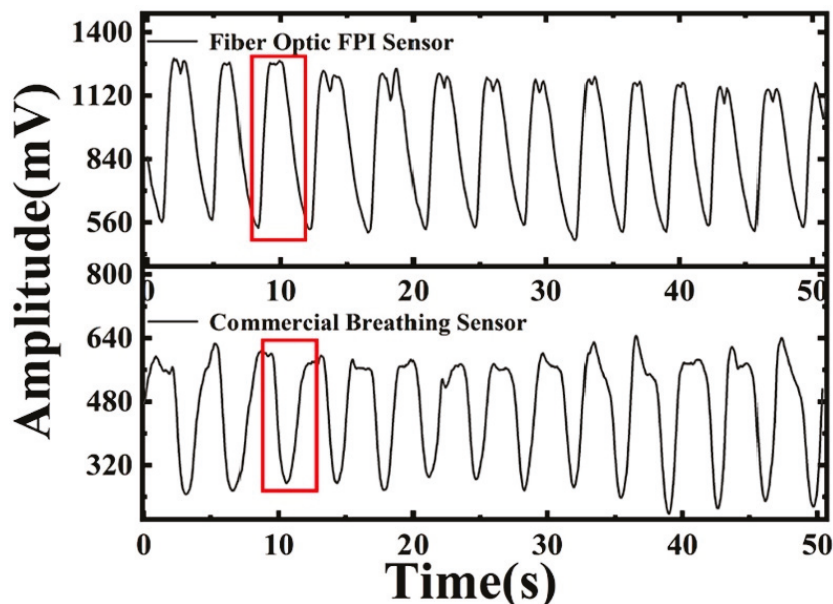
### 3.2.3. Stimuli-Responsive Polymers

Stimuli-responsive polymers, also known as smart polymers, are a class of polymers that can undergo reversible changes in their physical or chemical properties in response to external stimuli, such as temperature, pH, light, or magnetic fields. These polymers have gained significant attention in the field of sensor fabrication due to their ability to provide a switchable or tunable response to the analyte of interest.

The most commonly used stimuli-responsive polymers for LbL assembly include poly(N-isopropylacrylamide) (PNIPAM) [87], which exhibits a temperature-responsive phase transition, and PAA and PMAA [88], which exhibit a pH-responsive swelling behavior. Other stimuli-responsive polymers, such as spiropyran-containing polymers and azobenzene-containing polymers [89–92], have also been used in the fabrication of LbL-based sensors. The LbL assembly of stimuli-responsive polymers can be used to create

smart or adaptive sensors that can respond to changes in the environment or the presence of specific analytes. For example, a temperature-responsive sensor based on PNIPAM can be used to monitor the temperature of a solution or a surface [93], while a pH-responsive sensor based on PAA or PMAA can be used to monitor the pH of a solution or a biological fluid [94].

Several studies have demonstrated the use of stimuli-responsive polymers in the fabrication of LbL-based sensors. For example, Xia et al. [95] recently developed a novel fiber-optic Fabry–Perot (FPI) sensor designed for highly sensitive relative humidity measurements, leveraging the unique properties of PNIPAM hydrogel. This sensor marked a significant advancement in humidity sensing technology, primarily due to the incorporation of PNIPAM hydrogel, which undergoes substantial physical changes in response to variations in humidity levels (Figure 10). These changes, particularly in the hydrogel's refractive index and volume, directly influence the sensor's optical properties, enabling precise humidity measurements. The sensor demonstrated exceptional performance metrics, including a high sensitivity of 1.634 nm/%RH within a relative humidity range of 45% to 75%. Moreover, the study highlighted the sensor's potential for wearable applications, such as respiratory monitoring, by showcasing its fast response and recovery times, which were crucial for real-time monitoring tasks. The incorporation of LbL assembly techniques further enhanced the sensor's functionality by improving the hydrogel's structural integrity and sensitivity to humidity changes. Liu and Cui [96] developed and analyzed a pH sensor utilizing an ion-sensitive field-effect transistor (ISFET), leveraging the LbL self-assembly method. This innovative approach incorporated polyelectrolyte/nanoparticle multi-layer films to construct the device, focusing on the use of PMMA and the LbL technique for enhanced performance. PMMA was specifically applied to minimize gate leakage current, significantly improving the device's operational stability. The sensor demonstrated a pronounced sensitivity to pH variations, with the drain current notably decreasing as the pH value increased, showcasing its efficiency in acidic conditions. The mobility of the ISFET, recorded at 35.68 cm<sup>2</sup>/Vs at room temperature, was found to increase with temperature, suggesting a positive correlation between temperature and carrier mobility.



**Figure 10.** Partial enlarged view of the respiratory response monitored by the fabricated FPI sensor [95].



## 4. LbL-Fabricated Wearable Sensors for Health Monitoring

### 4.1. Physical Sensors

Physical sensors are devices that detect and measure physical quantities, such as strain, pressure, temperature, and light, and convert them into electrical or optical signals. These sensors have gained significant attention in the field of wearable health monitoring due to their ability to provide real-time and non-invasive information about the physiological status and activity of the human body. In this section, we will discuss the use of LbL-fabricated physical sensors, including strain and pressure sensors, temperature sensors, and optical sensors, for various applications in wearable health monitoring. Table 1 summarizes recent several reports of physical sensors prepared via LbL method.

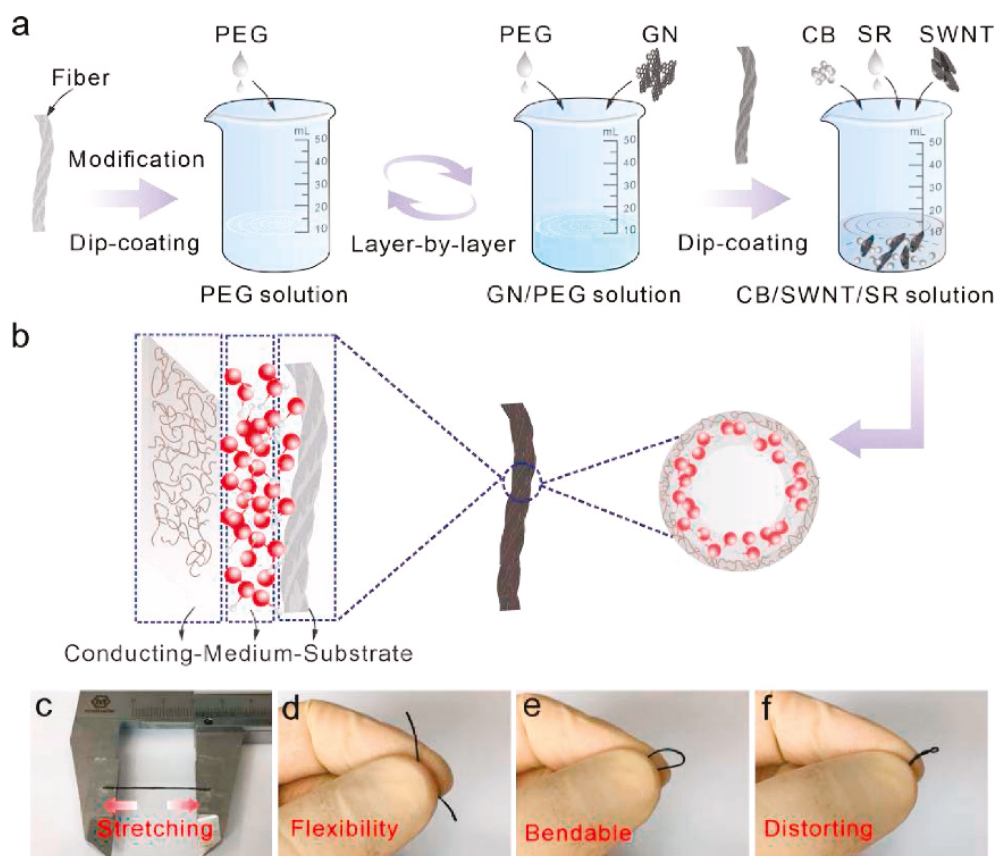
**Table 1.** Physical sensors prepared via LbL method and their performance.

| Sensor Component                                                                                                              | Performance                                                                        | Reference |
|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------|
| <b>Strain and Pressure Sensors</b>                                                                                            |                                                                                    |           |
| Polymer used: PDDA; PSS<br>Conductive materials: graphene                                                                     | Gauge factor: 78.13                                                                | [97]      |
| Polymer used: polyurethane; polyethylene glycol<br>Conductive materials: graphene nanoplatelets; carbon black; silicon rubber | Gauge factor: 2.0 at 50% strain<br>Response time: 60 ms<br>Durability: 3000 cycles | [98]      |
| Polymer used: PDMS<br>Conductive material: CNT                                                                                | Gauge factor: 35.75<br>Stretchability: up to 45%                                   | [99]      |
| Polymer used: polyurethane yarn; PDMS<br>Conductive material: graphene nanosheets; thin gold film                             | Gauge factor: 661.59<br>Durability: applied strain of 50% for 10,000 cycles        | [100]     |
| Polymer used: polyaniline fiber<br>Nanocomposite material: MXene sheets                                                       | Gauge factor: 2369.1<br>Stretchability: up to 80%                                  | [101]     |
| <b>Temperature Sensors</b>                                                                                                    |                                                                                    |           |
| Polymer used: PDDA; PAA<br>Conductive materials: CdSe quantum dots                                                            | Detection range: −40–70 °C                                                         | [102]     |
| Polymer used: polyacrylonitrile<br>Conductive materials: GO                                                                   | Detection range: 20–100 °C<br>Sensitivity: −0.4%/°C                                | [103]     |
| Polymer used: polyacrylonitrile                                                                                               | Detection range: 15–50 °C                                                          | [104]     |
| <b>Optical Sensors</b>                                                                                                        |                                                                                    |           |
| Polymer used: PAH<br>Counterpart material: BY                                                                                 | pH range: 6.80 to 9.00<br>Wavelength shift: 4.65 nm per 0.2 pH units               | [105]     |
| Polymer used: PAH<br>Counterpart material: SiO <sub>2</sub>                                                                   | pH range: 6.00 to 9.00                                                             | [106]     |
| Polymer used: PAH; PAA<br>Counterpart material: AuNPs                                                                         | RH range: 20 to 80%                                                                | [107]     |

#### 4.1.1. Strain and Pressure Sensors

Strain and pressure sensors are devices that detect and measure the mechanical deformation or force applied to a surface. These sensors have been widely used in wearable health monitoring for applications such as motion tracking, posture detection, and pulse monitoring. The LbL assembly technique has been used to fabricate strain and pressure sensors with high sensitivity, flexibility, and durability, by combining functional materials such as CNT, graphene, and metal nanoparticles with polymeric matrices. For example, Zhang et al. [97] developed a flexible strain sensor using a LbL self-assembly technique to fabricate a graphene/poly(diallyldimethylammonium chloride) (PDDA) nanocomposite film on flexible substrates. The sensor's strain-sensing properties were thoroughly investigated, revealing an excellent response, reversibility, and repeatability to various levels of deformation. Specifically, the sensor exhibited a sensitivity increase of up to 1% under a

deflection of 500  $\mu\text{m}$ , with an almost instantaneous response time. Additionally, the sensor demonstrated outstanding stability over 20 days without significant variation in sensitivity under different deflections (100  $\mu\text{m}$ , 300  $\mu\text{m}$ , and 500  $\mu\text{m}$ ). The study attributed the strain-sensing mechanism to the electrical resistance change caused by the piezoresistive effect, enhanced by the unique hierarchical nanostructure formed through electrostatic action between carboxylated graphene and PDDA. In another study, Guo et al. [98] developed a biomimetic flexible strain sensor inspired by the lateral line scale of fish, incorporating a novel double conducting layer design. Through a meticulous LbL dip-coating process, the sensor achieved a unique conducting-medium-substrate structure, which significantly enhanced its performance metrics (Figure 11). The sensor demonstrated exceptional linearity, with specific data revealing its capability to maintain consistent performance across varying strains, a critical feature for applications requiring precise motion detection. The double conducting layers, composed of graphene nanoplatelets (GN) for the interior and a carbon black/SWCNT (CB/SWNT) mix for the lateral layer, were pivotal in achieving this high linearity. This was evidenced by the sensor's ability to accurately measure strain with minimal deviation, showcasing linearity values ( $R^2$ ) exceeding 0.992 across different tensile states. Furthermore, the sensor's dynamic response was highlighted by its fast response time of approximately 60 ms and its durability, maintaining stability over 3000 cycles of use.



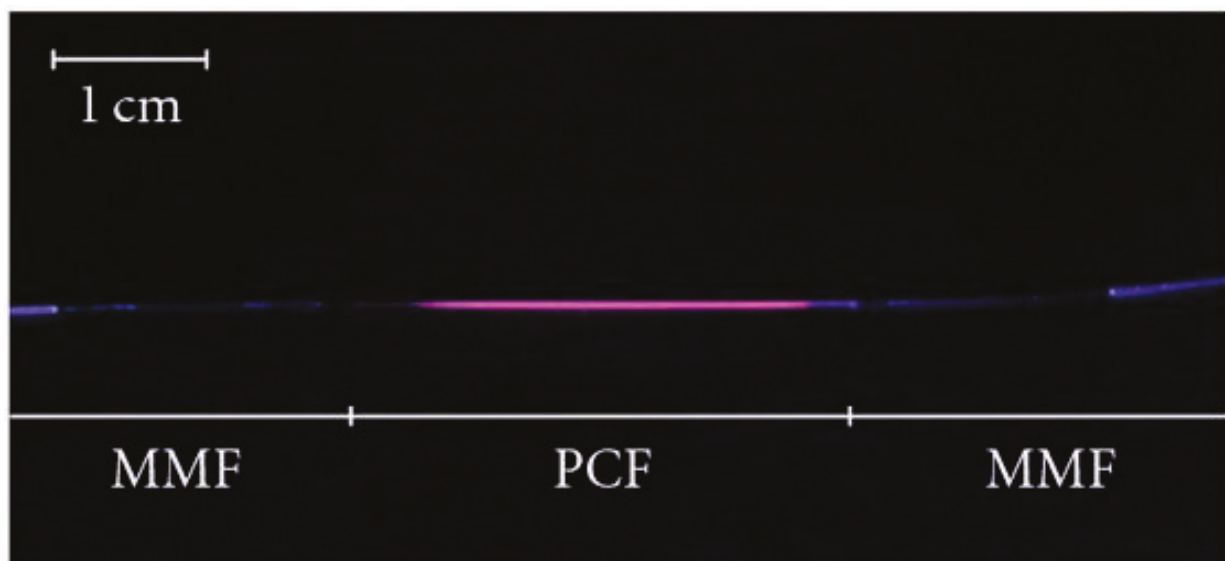
**Figure 11.** (a) Fabrication processes of biomimetic flexible strain sensor. (b) The sensing framework of conducting-medium-substrate for the strain sensor. (c–f) Optical graphs of the strain sensor, demonstrating high flexibility, good bendability [98].

#### 4.1.2. Temperature Sensors

Temperature sensors are devices that detect and measure the thermal energy or temperature of an object or environment. These sensors have been widely used in wearable health monitoring for applications such as body temperature monitoring, fever detection, and heat stress prevention. The LbL assembly technique has been used to fabricate tem-

perature sensors with high sensitivity, stability, and biocompatibility, by incorporating thermoresponsive polymers or nanoparticles into the multi-layer films.

For example, Larrión et al. [102] explored the development of a temperature sensor through the innovative use of quantum dot (QD) nanocoatings applied inside the hollow structures of photonic crystal fibers (PCFs) utilizing a LbL technique (Figure 12). This method involved alternating layers of positively charged PDDA and negatively charged PAA, followed by the incorporation of QDs, to meticulously control the nanofilm's thickness and enhance sensor performance. The primary focus was on the unique optical properties of QDs, which shift in emission wavelengths and intensities with temperature changes, making them ideal for precise temperature sensing. The sensor's performance was tested across a temperature range, showcasing its ability to detect shifts through changes in the optical absorption and emission characteristics of the QDs. Specifically, the absorption studies revealed a decrease in absorbance with rising temperatures, fitting an exponential curve with high correlation, indicating the sensor's effective response to temperature changes. Similarly, emission studies highlighted a decrease in emission intensity and a shift to higher wavelengths as temperatures increased, with data fitting an exponential model that underscored the sensor's high sensitivity and precision. The average sensitivity of this novel sensor was remarkable, with specific performance metrics indicating its potential superiority over traditional temperature measurement methods in terms of responsiveness and accuracy. Ke et al. [103] developed a method for fabricating all-graphene coated conductive fibers, leveraging a LbL assembly technique. This innovative approach utilized positively charged GO as a pivotal adhesive layer, significantly boosting the conductivity of the fibers. The core purpose of employing the LbL method was to enhance the fibers' stability and performance, particularly for applications in smart textiles. The study revealed that this technique markedly improved the fibers' resistance to water washing and mitigated their temperature sensitivity and dependence on environmental humidity. Mahadeva et al. [104] developed a temperature sensor utilizing a LbL assembly technique. The sensor exhibited a rapid response time, with the ability to detect temperature changes within seconds, and showcased an impressive sensitivity, accurately capturing fluctuations as minute as 0.1 °C. Furthermore, the sensor's durability was tested, revealing its ability to maintain consistent performance over thousands of temperature cycles, indicating its potential for long-term applications.



**Figure 12.** Picture of the LMA20 segment spliced to the MMF fibers under UV illumination [102].

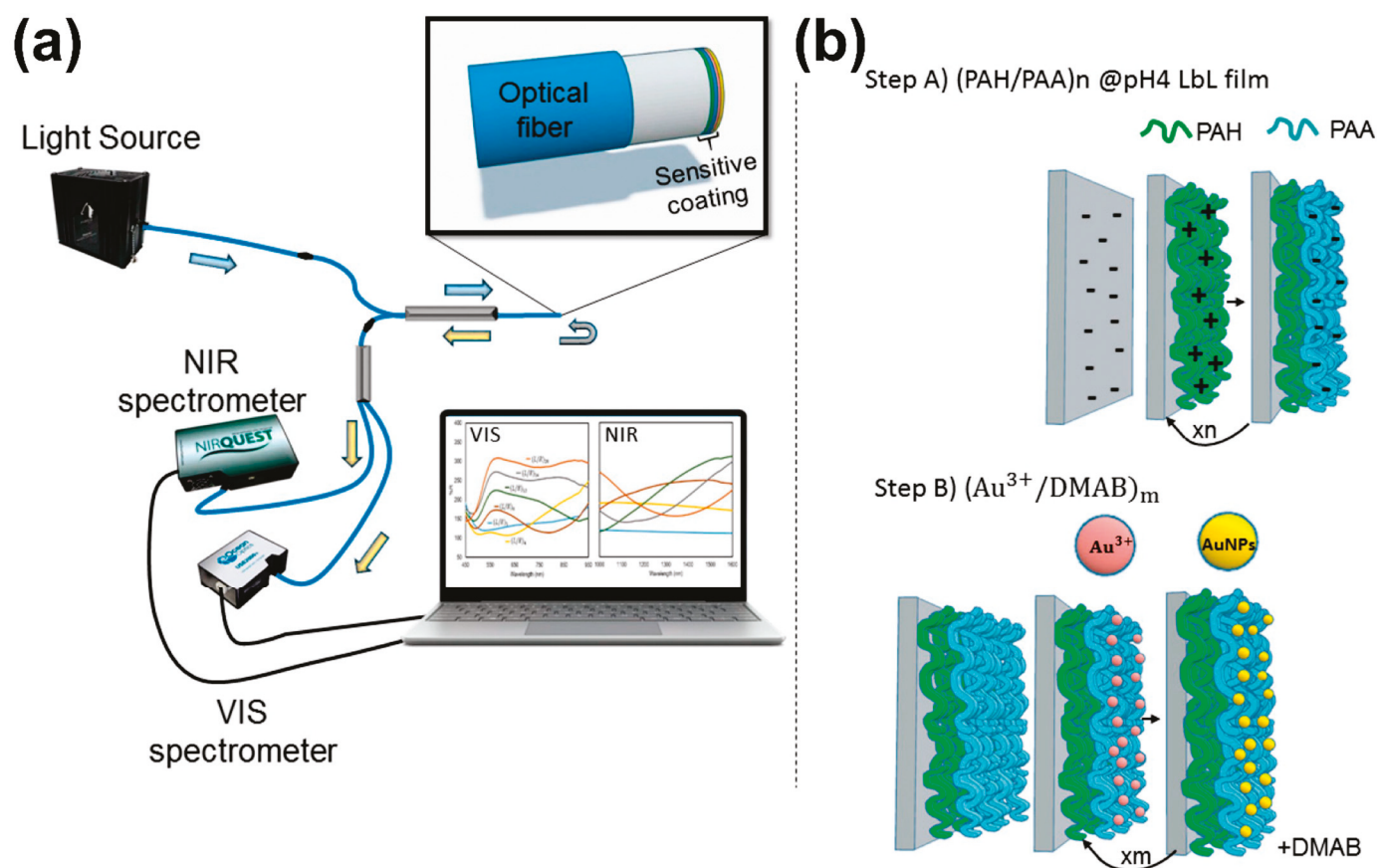
#### 4.1.3. Optical Sensors

Optical sensors are devices that detect and measure the optical properties, such as absorption, emission, or scattering, of a sample or analyte. These sensors have been widely used in pH analysis. The LbL assembly technique has been used to fabricate optical sensors with high sensitivity, selectivity, and miniaturization, by incorporating optically active materials, such as quantum dots, plasmonic nanoparticles, and fluorescent dyes, into the multi-layer films.

For example, Raoufi et al. [105] developed a wavelength-dependent pH optical sensor utilizing a LbL technique. By depositing brilliant yellow (BY) and PAH onto an optical fiber core, they crafted a sensor with remarkable sensitivity to pH changes. The study revealed that the sensor's dissociation constant varied with the outer layer and the number of bilayers, highlighting the LbL technique's role in fine-tuning the sensor's responsiveness. A pivotal finding was that sensors with six double layers of PAH/BY exhibited optimal sensitivity within a pH range of 6.80 to 9.00, achieving an accuracy of  $\pm 0.20$  and demonstrating an average wavelength shift of 4.65 nm per 0.2 pH unit change. This precision was attained while maintaining BY and PAH solution concentrations at 0.25 mM and 2.5 mM, respectively. In another study [106], they focused on improving the stability and re-usability of optical pH sensors by employing a LbL deposition technique. The team compared three stabilization methods: heat treatment, and the application of PAH/SiO<sub>2</sub> and APTMS/SiO<sub>2</sub> bilayers. Among these, the APTMS/SiO<sub>2</sub> bilayer approach significantly outperformed the others, leading to a notable improvement in the sensor's performance metrics. The sensors augmented with APTMS/SiO<sub>2</sub> bilayers demonstrated exceptional stability and re-usability, maintaining accurate calibration and reproducibility across multiple cycles of use.

Martínez-Hernández et al. [107] enhanced the interferometric response of optical fiber sensors by synthesizing AuNPs within a polymeric thin film through the in situ synthesis (ISS) technique. This process involved first constructing a polymeric coating on the optical fiber using a LbL assembly technique, followed by the synthesis of AuNPs directly within this polymeric matrix (Figure 13). The purpose of employing LbL was to create a stable, charged environment that could effectively support the growth and retention of AuNPs. The main results highlighted the critical role of the LbL assembly in optimizing the sensor's performance. Specifically, sensors with 25 (PAH/PAA) bilayers exhibited a stronger violet coloration and higher absorbance values compared to those with 15 bilayers, indicating a denser and more effective nanoparticle incorporation. Furthermore, increasing the number of loading/reduction cycles led to a noticeable enhancement in the optical absorption band, achieving an intense peak at 550 nm, characteristic of AuNPs. Esfahani et al. [108] developed a flexible electrochemical solid-state sensor designed for the detection of aluminum ions (Al<sup>3+</sup>), leveraging the unique properties of layered double hydroxide (LDH) nanoplatelets and alizarin red S (ARS) within a matrix film on an indium tin oxide/PET (ITO/PET) electrode. This sensor demonstrated exceptional sensitivity and selectivity towards Al<sup>3+</sup> ions, achieving a lower detection limit of 10.1 nM and a linear response range from 0.2 to 120  $\mu$ M. A pivotal aspect of this research was the utilization of a LbL assembly method to modify the sensor's surface, which significantly enhanced its performance. Each LbL cycle resulted in an increased density of LDH layers, which in turn amplified the surface roughness and thickness of the electrode.





**Figure 13.** (a) Experimental setup and (b) schematic illustration of the LbL nano-assembly built-up and a further ISS of the AuNPs into the previously created LbL films [107].

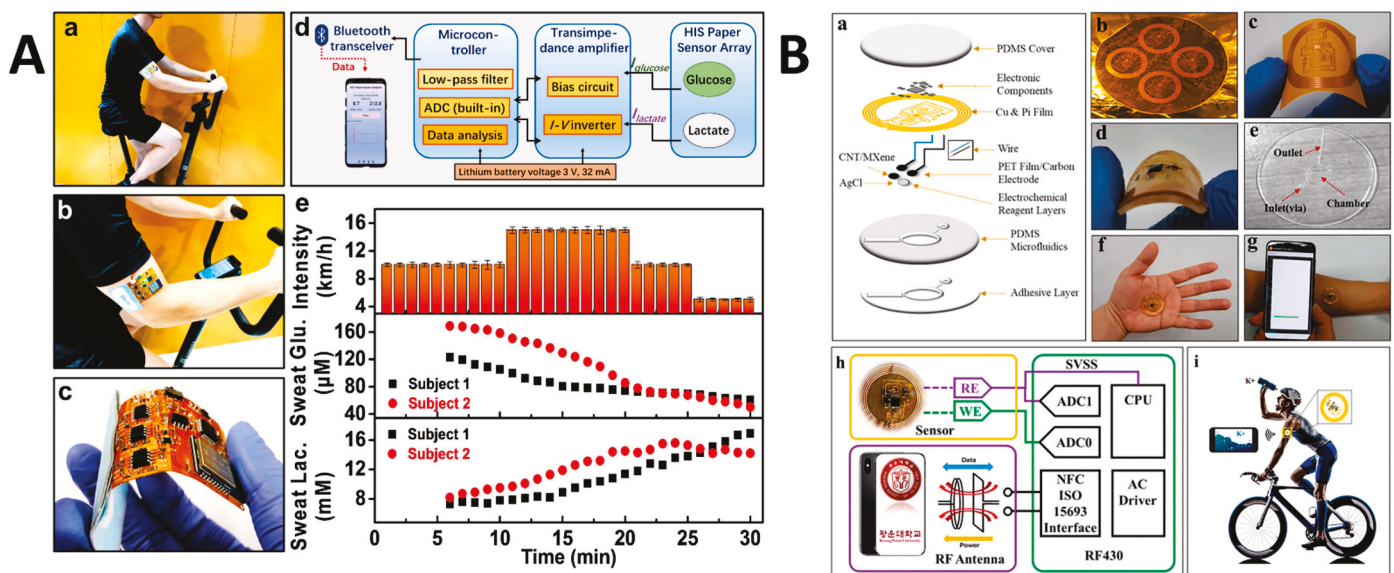
#### 4.2. Chemical Sensors

Chemical sensors are devices that detect and measure the presence and concentration of specific chemical species, such as ions, molecules, or gases, in a sample or environment. These sensors have gained significant attention in the field of wearable health monitoring due to their ability to provide valuable information about the chemical composition and status of various bodily fluids, such as sweat, saliva, and interstitial fluid.

Electrochemical sensors are devices that detect and measure the electrochemical properties, such as current, potential, or impedance, of a sample or analyte. These sensors have been widely used in wearable health monitoring for applications such as glucose monitoring, lactate monitoring, and drug detection. The LbL assembly technique has been used to fabricate electrochemical sensors with high sensitivity, selectivity, and stability, by incorporating functional materials, such as enzymes, nanoparticles, and conductive polymers, into the multi-layer films [109]. For example, Li et al. [110] developed a highly integrated sensing paper designed for the real-time monitoring of sweat, focusing particularly on glucose and lactate levels. This innovative paper-based sensor leveraged a three-dimensional structure to enhance sweat absorption and ensure the stability of its embedded electrodes. A key aspect of the sensor's design was the use of LbL assembly to functionalize the working electrodes, which significantly improved the sensor's sensitivity and specificity towards glucose and lactate detection (Figure 14A). The paper demonstrated remarkable performance in detecting these biomarkers, with sensitivities reaching 2.4 nA/Mm for glucose and 0.49  $\mu$ A/mM for lactate. The purpose behind employing LbL assembly was to create a sensor that could provide accurate and reliable monitoring of key sweat biomarkers in a non-invasive manner. The effectiveness of this approach was evident in the sensor's ability to rapidly and efficiently analyze sweat composition, offering a promising tool for health monitoring and disease prevention. In another study, Zhang



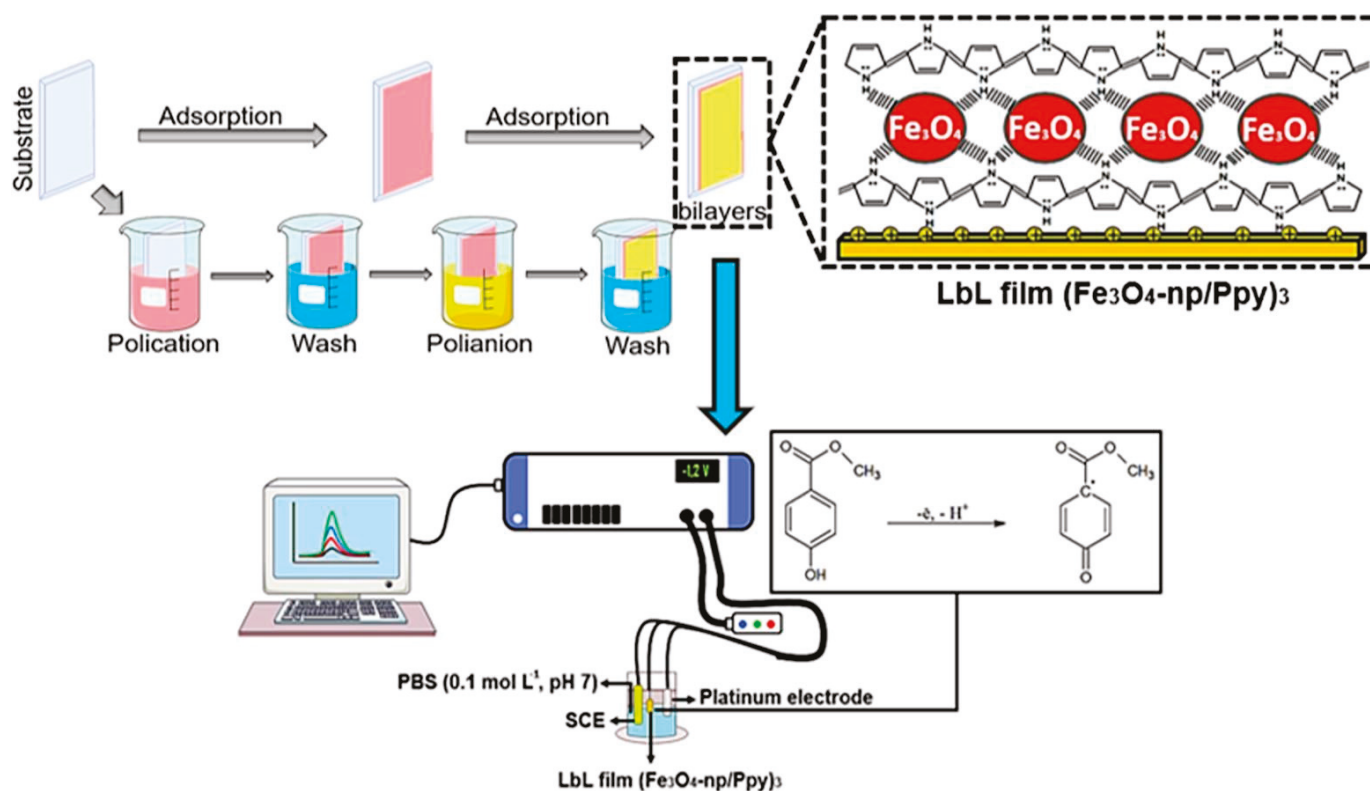
et al. [111] developed a wearable, battery-free, and wireless skin-interfaced microfluidic patch that integrates electrochemical sensing for the real-time monitoring of biomarkers in human sweat. Central to this innovation was the employment of LbL assembly techniques, which utilized MWCNT and MXene-Ti<sub>3</sub>C<sub>2</sub>T<sub>x</sub> hybrid networks. This strategic combination significantly amplified the sensitivity and stability of the sensor, enabling precise biomarker detection (Figure 14B). The patch featured a microfluidic channel design that efficiently collected and directed sweat to the sensing area, ensuring accurate and consistent analysis. The main results highlighted the patch's exceptional performance in monitoring potassium ion concentration in human sweat, a critical biomarker for various physiological conditions. Through rigorous testing, the sensor demonstrated a rapid response time and a wide linear range for potassium ion detection. The sensor's potentiometric response to potassium ions was evaluated, revealing a high degree of selectivity against potential interfering species such as Zn<sup>2+</sup>, Na<sup>+</sup>, and Ca<sup>2+</sup>. This specificity underscored the sensor's capability to provide reliable data in complex biological fluids like sweat. In application, the patch's performance was validated through on-body tests, where it successfully monitored potassium ion concentration levels during physical activities.



**Figure 14.** (A) Real-time on-body evaluation of the paper-based sweat monitoring system. (a) The photograph of the sweat analysis with the paper-based system mounted on the arm during physical activity. (b) The detection process with the wireless patch to receive the detection data and display the results. (c) Detailed photograph of the flexible circuit board. (d) Illustration of the analysis system. (e) The real-time concentration curve of sweat glucose (Glu.) and sweat lactate (Lac.) of volunteers during cycling with corresponding exercise intensities [110]. (B) (a) Schematic illustrating the exploded view of the wireless, battery-free, flexible, microfluidic/electronic system. (b,c) The lithography and etching process is used to make the flexible antenna and circuits. (d) Encapsulation of flexible circuits with PDMS. (e) The microfluidic system. (f) A very light and small-sized circular patch sensor system. (g) Wireless NFC sensor and smartphone communication in real time. (h) Electronics design, measurement strategy, and complete system. (i) Measuring the electrolyte losses from athletes' sweat could help health professionals plan personalized water and electrolyte replacement strategies [111].

LbL technology has also been used for the construction of other non-human electrochemical sensing purposes. De Lima et al. [112] developed an electrochemical sensor for detecting methylparaben (MeP), utilizing a LbL films of magnetite nanoparticles (MNP) and Ppy onto gold electrodes (Figure 15). Empirical results from the study indicated that the optimized sensor, featuring the Au/(MNP/Ppy)<sub>3</sub> architecture, achieved a notably low detection limit of  $9.95 \times 10^{-8}$  M and a broad detection range up to 131.4  $\mu$ M for MeP. More-

over, when tested with real-world samples such as urine, breast milk, and cosmetics, the sensor not only maintained its high performance but also yielded recovery rates between 84.0% and 113.3%. In a recent study [113], they also fabricated an electrochemical sensor for detecting propylparaben by constructing a LbL film. This film was meticulously assembled on an ITO electrode, integrating AuNPs, PEI, and nickel(II) phthalocyanine tetrasulfonate (NiTsPc). The sensor exhibited an impressive limit of detection, with a notable sensitivity that could be attributed to the synergistic effect of the materials used in the LbL film. In another study, Morais et al. [114] developed an EIS sensor modified with a LbL film for detecting  $\text{Pb}^{2+}$  and  $\text{Ni}^{2+}$  ions. This film was assembled by alternating layers of PAA and PVP, incorporating  $\text{Sn}_3\text{O}_4$  nanobelts within the structure. The final sensor demonstrated high sensitivity and selectivity in detecting  $\text{Pb}^{2+}$  and  $\text{Ni}^{2+}$  ions, with a detection limit for  $\text{Pb}^{2+}$  at  $0.17 \mu\text{M}$  ( $34 \mu\text{g/L}$ ).



**Figure 15.** LbL films of magnetite nanoparticles and Ppy towards methylparaben electrochemical detection [112].

## 5. Applications of LbL-Fabricated Wearable Sensors

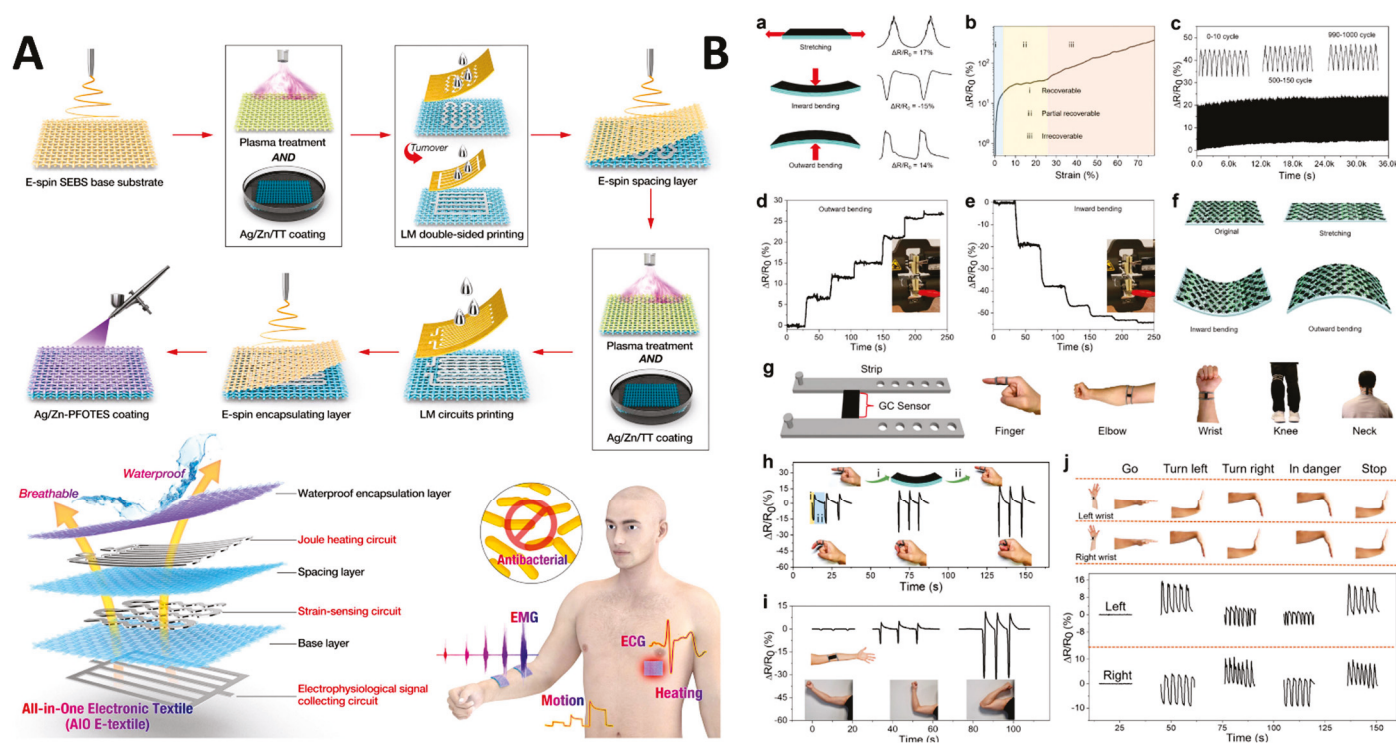
LbL-fabricated wearable sensors have found numerous applications in various fields, ranging from healthcare and fitness to environmental monitoring. The unique features of LbL-fabricated sensors, such as their flexibility, biocompatibility, and versatility, make them ideal for wearable applications that require continuous and non-invasive monitoring. In this section, we will discuss the main applications of LbL-fabricated wearable sensors, including continuous health monitoring and disease diagnosis and management.

### 5.1. Continuous Health Monitoring

Continuous health monitoring involves the real-time and non-invasive measurement of various physiological parameters, such as heart rate, blood pressure, body temperature, and respiration rate, using wearable sensors. LbL-fabricated sensors have been widely explored for continuous health monitoring applications due to their ability to conform to the skin and provide accurate and reliable measurements. These sensors can be integrated

into various wearable platforms, such as patches, bandages, and clothing, allowing for the seamless and unobtrusive monitoring of health status [115–118].

For example, Peng et al. [119] developed an innovative hierarchical and ultrastretchable all-in-one electronic textile (AIO E-textile) designed for health regulation (Figure 16A). This multi-functional textile, constructed from a breathable nonwoven material, was engineered to integrate various health monitoring and environmental protection features. Key to its design were the antibacterial and waterproof surfaces, achieved through the incorporation of Ag/Zn nanoparticles and a superhydrophobic layer, ensuring both durability against liquid infiltration and a healthy microenvironment for the skin. The textile featured embedded liquid metal circuits for real-time monitoring of bioelectrical signals such as electrocardiograms (ECG) and surface electromyography (sEMG), demonstrating exceptional fidelity in signal recording. Additionally, the AIO E-textile showcased a low-watt Joule heating capability for thermal regulation, alongside rapid strain sensing and superior underwater motion detection capabilities. The successful integration of these features, including a water contact angle exceeding  $150^\circ$  after prolonged exposure to harsh conditions and antibacterial efficacy maintaining over 99.99% inactivation of *E. coli* post-extensive-washing, marks a significant advancement in wearable health technologies.



**Figure 16.** (A) Schematic for the fabrication of the AIO E-textile. Illustration for the detailed configuration of designed AIO E-textile with integrated functionalities [119]. (B) (a) Detection signals of the GC sensor under different deformations; (b) change in normalized resistance against strain; (c) cyclic test results of 1000 stretch–release cycles of the GC sensor tensile bar with 5% elongation; the GC sensor monitors the response signals of (d) outward bending and (e) inward bending; (f) schematic illustration of the changes in the conductive layer under external forces; (g) the design and applications of the printed GC sensors; output signals of the GC sensor collected at the bending of (h) finger and (i) elbow; (j) discrimination of emergency signs based on two GC sensors worn on both wrists [120].



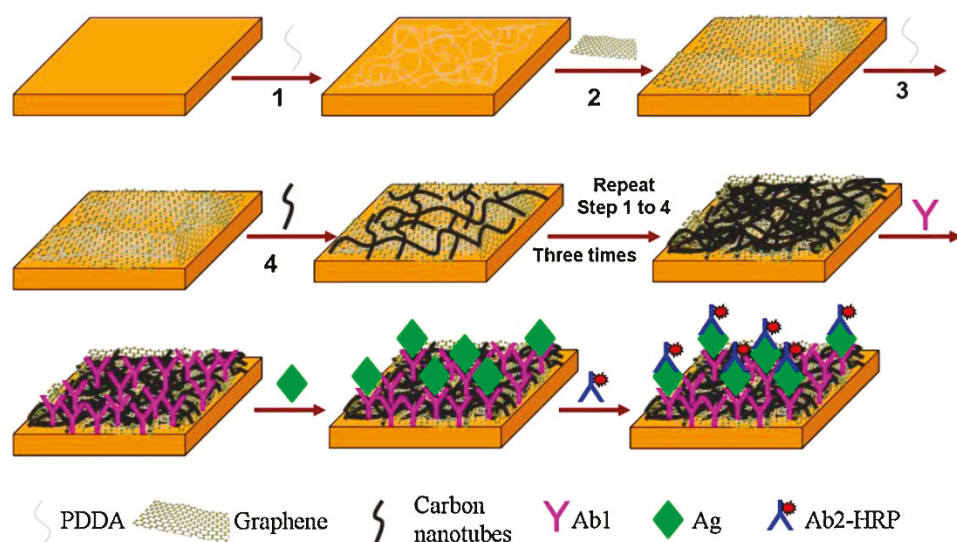
In another study, Hou et al. [120] developed and tested 3D printed conformal strain and humidity sensors using a novel graphene/CNT (GC) ink, aimed at enhancing human motion prediction and health monitoring. The innovative approach leveraged multi jet fusion (MJF) printing technology to fabricate sensors that exhibit remarkable flexibility, durability, and conformity to human skin, making them ideal for wearable applications. The sensors demonstrated high sensitivity to both strain and humidity changes, with the ability to accurately detect and monitor a wide range of human motions, including sitting down, climbing stairs, squatting, running, walking, and jumping (Figure 16B). A key aspect of the study was the use of machine learning algorithms, particularly support vector machines (SVM), to analyze data collected from the sensors. The SVM was trained with features extracted from the sensor data, achieving an impressive motion prediction accuracy of 95.83% for both linear and polynomial kernel functions. Furthermore, the research highlighted the superiority of the GC ink used in the printing process. This ink exhibited excellent printability and stability, enabling the creation of conductive paths essential for the sensor's functionality. The multi-layered structure of the sensors, inspired by natural phenomena such as peacock feathers and butterfly wings, played a crucial role in their performance by enhancing their mechanical and sensing properties.

### 5.2. Disease Diagnosis and Management

Disease diagnosis and management involve the use of wearable sensors for the early detection, monitoring, and treatment of various diseases, such as diabetes, cardiovascular disorders, and cancer [121]. LbL-fabricated sensors have shown great potential for disease diagnosis and management applications due to their ability to detect specific biomarkers and bioreceptors with high sensitivity and selectivity. These sensors can be integrated into wearable platforms that are easy to use, painless, and economical, enabling the rapid and reliable diagnosis and management of diseases.

For example, Nag et al. [122] explored the potential of a novel sensor design for detecting volatile organic compounds (VOCs), crucial for early disease diagnosis, including cancer. Central to this innovation was the use of a LbL assembly method to functionalize CNT with polyhedral oligomeric silsesquioxanes (POSS), enhancing the sensor's sensitivity and selectivity towards specific VOC biomarkers. The LbL technique allowed for precise control over the sensor surface properties, resulting in the ability to fine-tune the sensor's response to various VOCs. Performance tests revealed that these sensors could detect VOC concentrations in ppm, with some configurations achieving sensitivity in ppb, showcasing their exceptional resolution. The study meticulously evaluated the sensors' limit of detection, employing a signal-to-noise ratio (SNR) criterion for assessing efficiency at ppm to ppb levels of VOC presence. The sensors demonstrated a marked improvement in detecting and discriminating between different VOCs, attributed to the POSS-functionalized CNTs' unique properties. The POSS molecules, when grafted onto the CNT surface, not only increased the thermal stability of the sensors but also significantly boosted their chemo-resistive behavior, enabling a more robust and reliable detection of VOC biomarkers. Chang et al. [123] developed an electrochemical biosensor utilizing a LbL assembly technique to quantitatively evaluate oxidative stress in tumor cells through the detection of  $H_2O_2$  release. This biosensor incorporated rGO, Au NPs, and poly(toluidine blue O) (PTBO) films, leveraging the unique properties of each material to enhance sensitivity and selectivity towards  $H_2O_2$ . The study's pivotal findings revealed that tumor cells emitted  $H_2O_2$  at significantly higher levels than normal cells, underscoring the heightened oxidative stress within tumor environments. Specifically, the sensor's performance was highlighted by its ability to detect  $H_2O_2$  with high precision, demonstrating a substantial increase in current response when tumor cells were analyzed compared to normal cells. Ai [124] explored the application of LbL self-assembled polyelectrolyte capsules for enhancing magnetic resonance imaging (MRI) diagnostics. The study meticulously demonstrated how these LbL capsules, when embedded with paramagnetic metal-ligand complexes or superparamagnetic iron oxide nanoparticles, significantly improved MRI

visibility and contrast, thus offering a promising avenue for more accurate and sensitive diagnostic imaging. Specifically, the capsules showcased an ability to provide detailed images by enhancing the contrast in areas of interest, which is critical for early detection and diagnosis of diseases. By integrating diagnostic and therapeutic functionalities, these LbL capsules pave the way for advancements in theranostics, offering a synergistic approach to disease management that combines diagnosis, therapy, and follow-up in one platform. Liu et al. [125] developed a sensitive electrochemical immunosensor for the detection of human immunoglobulin G (IgG). This innovative approach utilized a LbL assembly method to create a composite electrode interface, enhancing the electrochemical performance through the strategic application of PDDA (Figure 17). PDDA served a dual purpose: facilitating the layering process by forming a stable link between the negatively charged graphene and MWCTs, and significantly improving the electron transfer rate across the composite interface. The meticulous assembly resulted in an electrode that exhibited exceptional sensitivity and specificity in detecting human IgG, with a remarkable detection limit of 0.2 ng/mL. The immunosensor's performance was further validated through clinical tests, where it demonstrated excellent reproducibility, stability, and selectivity.



**Figure 17.** Schematic illustration of the fabrication of graphene-carbon nanotube electrode interface and the construction of the sandwich-type electrochemical immunosensor [125].

## 6. Challenges and Future Perspectives

Despite the significant advancements in the field of LbL-fabricated wearable sensors, there are still several challenges that need to be addressed to enable their widespread adoption and commercialization. These challenges include issues related to long-term stability and durability, biocompatibility and wearability, data acquisition and analysis, and large-scale manufacturing and commercialization. In this section, we will discuss these challenges in detail and provide insights into the future perspectives of LbL-fabricated wearable sensors.

One of the major challenges facing LbL-fabricated wearable sensors is their long-term stability and durability. Sweat composition varies among individuals and can be influenced by factors such as diet, hydration status, and physical activity. Moreover, the pH, ionic strength, and presence of interferents in sweat can fluctuate over time, which can affect the performance and reliability of the sensors. To address these issues, researchers are exploring the use of advanced materials, such as stimuli-responsive polymers and self-healing hydrogels, that can adapt to the changing sweat environment and maintain their functionality over extended periods. Additionally, the incorporation of protective coatings and encapsulation strategies can help to minimize the effects of sweat-induced degradation and biofouling on the sensor components. Another challenge facing LbL-fabricated wearable sensors is their biocompatibility and wearability. Wearable sensors are in direct



contact with the skin for prolonged periods, which can cause irritation, inflammation, and allergic reactions. LbL-fabricated sensors are particularly prone to these issues due to the potential for leaching of the materials and the presence of residual chemicals from the fabrication process. To address this challenge, researchers are exploring the use of biocompatible and non-toxic materials, such as natural polymers, hydrogels, and ceramics, for the fabrication of LbL-fabricated sensors. Mass production at low cost is another critical consideration for the commercialization of LbL-fabricated wearable sensors. While the LbL technique offers precise control over the sensor architecture and composition, it is inherently a time-consuming and labor-intensive process. To overcome this bottleneck, researchers are investigating the use of automated and scalable fabrication methods, such as spray-assisted LbL assembly and roll-to-roll processing, which can significantly reduce the production time and cost. Furthermore, the use of low-cost and abundant materials, such as cellulose and chitosan, can help to minimize the overall sensor cost without compromising performance. The susceptibility of sensor data to environmental disturbances, such as temperature and humidity, is another important challenge that needs to be addressed. Variations in ambient conditions can affect the sensor response and lead to inaccurate or unreliable measurements. To mitigate these effects, researchers are developing multi-modal sensing platforms that can simultaneously monitor multiple parameters, such as temperature and humidity, alongside the target analyte. By incorporating reference sensors and compensation algorithms, it is possible to correct for environmental disturbances and improve the accuracy and reliability of the sensor data.

A third challenge facing LbL-fabricated wearable sensors is the acquisition, transmission, and analysis of the sensor data. Wearable sensors generate large amounts of data that need to be collected, processed, and analyzed in real-time to provide meaningful insights into the wearer's health and well-being. However, the current data acquisition and transmission technologies, such as Bluetooth and Wi-Fi, are limited in terms of power consumption, data rate, and security. To address this challenge, researchers are exploring the use of low-power and high-bandwidth communication technologies, such as near-field communication (NFC) and ultra-wideband (UWB), for the wireless transmission of sensor data. Similarly, the use of edge computing and machine learning algorithms is being investigated for the real-time processing and analysis of sensor data on the wearable device itself, reducing the need for cloud computing and improving the privacy and security of the data. Finally, a significant challenge facing LbL-fabricated wearable sensors is their large-scale manufacturing and commercialization. LbL-fabricated sensors are currently limited to small-scale production in research labs, which is time-consuming, labor intensive, and expensive. To enable the widespread adoption and commercialization of LbL-fabricated sensors, there is a need for scalable and cost-effective manufacturing methods that can produce high-quality and reliable sensors in large quantities. To address this challenge, researchers are exploring the use of advanced manufacturing technologies, such as 3D printing, roll-to-roll processing, and automated LbL assembly, for the large-scale production of LbL-fabricated sensors.

Calibration is another critical aspect of translating raw sensor data into actionable information for health monitoring applications. Wearable sensors often require personalized calibration to account for inter-individual variability in sweat composition and skin physiology. However, this process can be time-consuming and inconvenient for users. To address this challenge, researchers are exploring the use of machine learning algorithms and artificial intelligence (AI) technologies to automate the calibration process and enable real-time data interpretation. By leveraging large datasets of sensor responses and corresponding physiological parameters, AI models can be trained to predict the target analyte concentrations directly from the raw sensor data, without the need for manual calibration. Moreover, AI can be used to identify patterns and correlations in the sensor data that may be indicative of specific health conditions or disease states, enabling early detection and intervention.

## 7. Conclusions

The recent advancements in polymer-assisted LbL fabrication of wearable sensors have opened up new possibilities for continuous health monitoring and disease diagnosis. LbL self-assembly has emerged as a powerful and versatile technique for creating conformal, flexible, and multi-functional films on various substrates, making it particularly suitable for fabricating wearable sensors. The incorporation of polymers, both natural and synthetic, has played a crucial role in enhancing the performance, stability, and biocompatibility of these sensors. Natural polymers, such as cellulose, chitosan, and silk fibroin, offer unique properties like biodegradability and biocompatibility, while synthetic polymers, including polyelectrolytes, conductive polymers, and stimuli-responsive polymers, provide tunability and functionality. LbL-fabricated wearable sensors have demonstrated exceptional capabilities in detecting and monitoring various physical, chemical, and biological parameters, enabling their applications in continuous health monitoring, disease diagnosis, and management. Despite the significant progress, challenges related to long-term stability, biocompatibility, data acquisition, and large-scale manufacturing still need to be addressed to realize the full potential of these sensors. Future research should focus on developing novel materials, optimizing the fabrication processes, and integrating advanced data processing and communication technologies to create reliable, cost-effective, and user-friendly wearable sensors. With continued advancements in polymer-assisted LbL fabrication and related fields, wearable sensors are poised to revolutionize personalized healthcare and improve the quality of life for individuals worldwide.

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## Review

# Recent Progress in Wearable Near-Sensor and In-Sensor Intelligent Perception Systems

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**Abstract:** As the Internet of Things (IoT) becomes more widespread, wearable smart systems will begin to be used in a variety of applications in people's daily lives, not only requiring the devices to have excellent flexibility and biocompatibility, but also taking into account redundant data and communication delays due to the use of a large number of sensors. Fortunately, the emerging paradigms of near-sensor and in-sensor computing, together with the proposal of flexible neuromorphic devices, provides a viable solution for the application of intelligent low-power wearable devices. Therefore, wearable smart systems based on new computing paradigms are of great research value. This review discusses the research status of a flexible five-sense sensing system based on near-sensor and in-sensor architectures, considering material design, structural design and circuit design. Furthermore, we summarize challenging problems that need to be solved and provide an outlook on the potential applications of intelligent wearable devices.

**Keywords:** functional sensor; near/in-sensor computing; flexible electronics; neuromorphic perception system

## 1. Introduction

With the rapid development of the Internet of Things (IoT), health monitoring devices such as armbands and glasses are becoming more intelligent and accurate. With the pressing need for high accuracy and real-time detection in medical applications, wearable and implantable devices are rapidly developing due to their advantages in directly collecting physiological information [1–11]. Through direct contact with the skin or even organs, wearable sensors can reduce the effect of interference and environmental noise compared to other general sensors. For wearable devices used in health monitoring, some characteristics should be fulfilled, including the following: (1) The device should have good stretching and bending properties to adapt to a range of human daily routines. (2) The device should have good biocompatibility to avoid skin irritation. (3) The device should be lightweight and comfortable to ensure comfort [12–17]. Recent research has shown that health monitoring devices have achieved high performance by integrating high-precision wearable sensors and computers [18–20]. However, redundant data being output from sensors is inevitable, and this causes a high transmission latency and power consumption to occur between sensors and computing units. To alleviate the shortcomings outlined above, a new computing paradigm proposes integrating some computing units into the sensing unit. Architecture differences and the classification of near/in-sensor computing can be distinguished by the degree of integration [21]. Zhou et al. referred to this part of

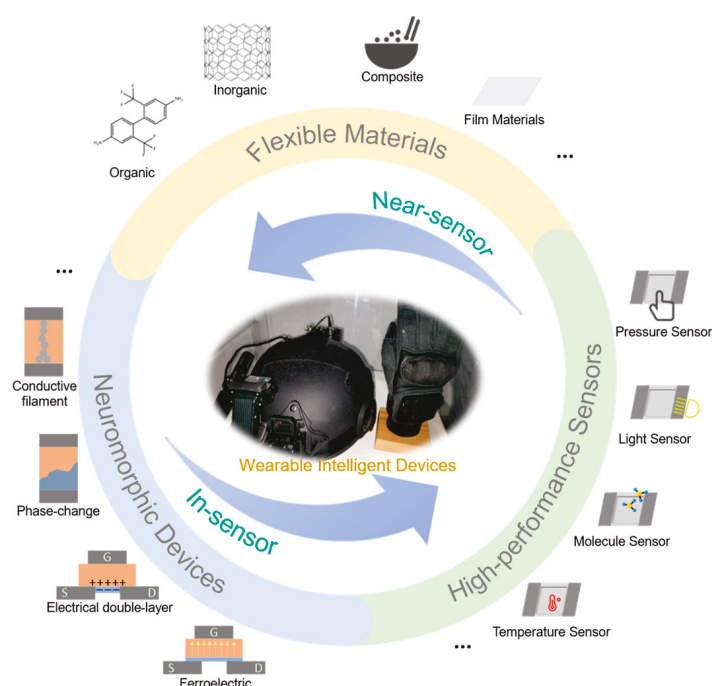
the computing unit as the front-end processing unit. The front-end processing unit can filter the redundant data and extract the effective data output from the sensors [22–24]. In addition, some researchers have proposed a variety of smart sensors that can perform summation operations by designing materials and structures, which are called in-sensor computing system [25–27]. As a new generation of smart sensor units, near/in-sensor computing systems have great potential for use in various applications, such as medical equipment, bionic robots and electronic skin.

Devices or circuits with information processing capabilities are required for the front-end processing unit. Memristors and synaptic transistors have emerged as the best choice for front-end processing units in near-sensor computing systems due to their ability to simulate the synapses of neurons [28,29]. If the postsynaptic current generated from redundant sensor data activated in near/in-sensor computing systems is not large enough, this means that it can be filtered out [30–32]. Until now, researchers have conducted systematic work on near/in-sensor computing systems, demonstrating the feasibility of tactile, visual, auditory and olfactory systems which use near/in-sensor computing [33–38]. However, hard bending or stretching is a general disadvantage in most of the recently proposed near/in-sensor computing systems due to their rigid electronic elements. The equipment used in health monitoring applications should be deformable and biocompatible. Therefore, the challenge of developing materials and electronic components which fulfill both good flexibility and biocompatibility still remains in this field. Additionally, research on memristors and synaptic transistors has primarily focused on rigid metal oxide materials due to the specific mechanisms of current neuromorphic devices. Recently, researchers have discovered the potential of near/in-sensor computing systems in edge computing and progress has been made in the flexibility of all components [39,40]. Due to their different working mechanisms, flexible sensors in system can be identified as piezoresistive, capacitive, piezoelectric or triboelectric sensors [41–44]. Filling a flexible medium layer with functional filler and depositing a film of functional materials on a flexible substrate are the two main methods of flexible material preparation. Carbon-based materials such as graphene, fullerene, C-nanotubes and carbon quantum dots have been more popular in recent research due to their excellent compatibility with elastic materials [45–48]. Additionally, metal powders or nanowires such as Cu, Au, Ag and Pt can be selected as functional fillers to confer electrical, magnetic or thermal properties to the functional medium layer. For instance, insulating materials can acquire conductive properties by being coated or mixed with conductive materials [49–51]. Notably, the combination of high-performance elastic materials and functional materials has emerged as a novel approach for fabricating high-performance flexible devices. Reducing the thickness of rigid functional materials such as ITO, mica and metal conductors is a method used to obtain stretching and bending properties. For example, metal oxide epitaxial thin films grown on flexible substrates also exhibit good flexibility [52–54]. In order to alleviate the concentration of stress, the thickness of rigid materials can be thinned, which can significantly reduce defects. In addition to the material used, designing special structures can also improve the performance of flexible sensors. Flexible sensors typically present an inferior mechanical performance and stability compared to rigid sensors; however, the introduction of microstructures such as pyramids, cylinders, half-spheres and wrinkles significantly enhances the resilience, stability and sensing capabilities of flexible sensors, which can be helpful for the development of high-performance flexible sensors [55–57]. Currently, the integration of material design and structural design is the most prevailing approach for designing flexible sensors in near/in-sensor systems.

Neuromorphic devices are an essential component of near/in-sensor systems due to their information-filtering ability and processing capabilities. Like flexible sensors, these devices require good flexibility and stability. Two completely different technical routes can be adopted for the fabrication of flexible memristors and synaptic transistors for use in the system. Flexible memristors are typically prepared by depositing electrodes and functional metal oxide films such as nickel oxide, hafnium oxide and titanium oxide directly

onto a flexible substrate [58–60]. Nevertheless, for synaptic transistors, researchers are exploring novel flexible functional materials, such as organic semi-conductors, graphene composites and bio-based materials, to replace the semi-conductor layer and substrate in conventional transistor structures [61–63]. Furthermore, there are intrinsic differences between memristors and synaptic transistors, influencing researchers' choices. Memristors can achieve higher integration densities due to their 2-terminal with a simple layered structure, while synaptic transistors offer a better design in terms of flexibility and stability due to their wide range of material selections and gate control mechanisms [64]. Flexible memristors and synaptic transistors have their own advantages in different applications. Research on near/in-sensor computing systems is still in the exploratory stage.

In conclusion, constructing a wearable near/in-sensor perception system is a complex task due to the incorporation of flexible materials, neuromorphic devices and high-performance sensors (Figure 1). Currently, the design of wearable near/in-sensor perception systems is mainly based on material selection and structural design because the tensile and flexural properties of the material can directly determine the flexibility and stability of the system, and the appropriate structural design can help to improve the performance of the components, and, thereby, the whole system. This review focuses on recent advancements in flexible sensors and neuromorphic devices' utility of near/in-sensor perception systems. Starting with the basic structure and working mechanism, we provide an overview of material design, structure design and near/in-sensor computing systems application. We summarize the main challenges in this sphere and provide an outlook on the application prospects of near/in-sensor computing systems. See Table 1.



**Figure 1.** Design thinking diagram for wearable near/in-sensor intelligent systems.

**Table 1.** Key parameters and functions of different systems.

| System Type | Key Parameter                      | Application                        |
|-------------|------------------------------------|------------------------------------|
| Tactile     | Sensitivity, detection range       | Pattern recognition                |
| Thalposis   | Detection range                    | Temperature perception, Assistance |
| Visual      | Detection limit, conversion rate   | Image recognition, assistance      |
| Olfactory   | Detection limit, molecular species | Molecular distinguishing           |
| Auditory    | Detection limit, frequency range   | Location, audio recognition        |



## 2. Near-Sensor and In-Sensor Computing System

In 2020, the research on near/in-sensor computing systems by Zhou et al. indicated that these systems are primarily designed to solve the problem of large amounts of redundant data being exchanged between sensory and computing units [21]. Compared to the conventional sensor–Analog-to-Digital convertor (ADC)–memory–backend architecture, the ADC and memory capabilities of sensory and computing units are replaced by neuromorphic devices in emerging near/in-sensor computing architectures. Neuromorphic devices such as memristors and synaptic transistors can be easily integrated into sensory units due to their simple structure. Additionally, these devices have an extremely low power consumption as they operate in a micro-current [23,65–67]. In addition to filtering, the ability neuromorphic devices to perform some information processing exists to some extent. In other words, neuromorphic devices can simulate synapse models to process information input. They have synaptic plasticity and nonvolatile characteristics which allow them to process specific voltage signals as input and store output in resistance form [68–70].

The relationship between near-sensor computing and in-sensor computing is progressive. A near-sensor computing system can filter redundant data at the sensing terminal by integrated the partial computing units near to the sensing units. This design significantly reduces the computing stress on computing units and the transmission consumption between sensing units and computing units. The necessity of a multi-functional sensing unit in in-sensor computing systems is to fulfil both ambient signals inputting and perform simple computing. This design eliminates the consumption caused by redundant data transmission. Neuromorphic devices can replace the ADC unit in near/in-sensor computing systems to decrease power consumption further by processing analog signals directly. Numerous experiments have demonstrated that integrating the neuromorphic computing paradigm with near/in-sensor architecture can significantly decrease power consumption by 1~2 orders of magnitude [71–73]. As a result, a neuromorphic device with a small size has better prospects for use in the self-powered devices in wearable technology [74].

## 3. Flexible Near-Sensor Artificial System

The sense organ system is a crucial part of the human body, acting as a primary interface between the body and the external environment. The human body's sense organ system can be broadly categorized into five types based on their working mechanisms: the tactile system (pressure and strain responsive), the temperature system (somatosensory), the visual system (light responsive), the auditory system (acoustic responsive) and the olfactory and gustatory system (molecular responsive) [75,76]. In comparison to artificial intelligence, the human nervous system is still more energy efficiency [77]. Near/in sensor systems, inspired by human sense organ system, have significant potential in the IoT. To create wearable near/in-sensor systems which are compatible with diverse signal inputs, flexible sensor fabrication often adopts material and structural design approaches. Diverse inputs have their counterpart outputs; therefore, matching sensors and front-end processing units can be a challenge in near/in-sensor computing systems design.

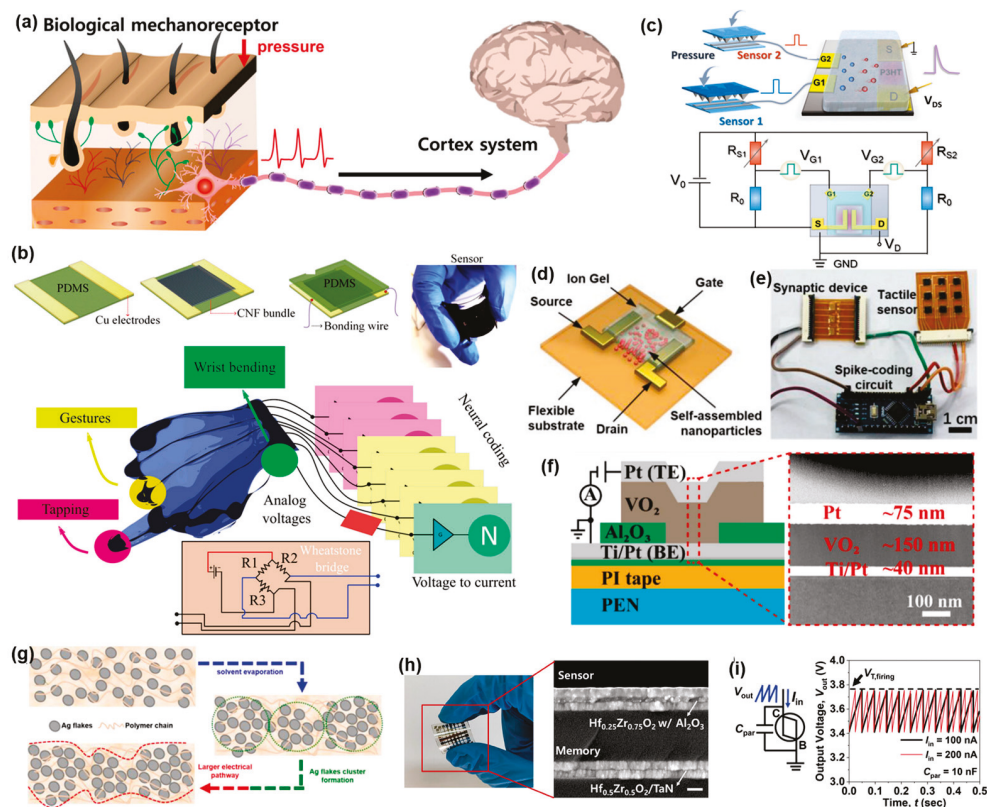
### 3.1. Flexible Near-Sensor Tactile System

The tactile system is a complex sensor organ system consisting of various receptors such as Pacinian corpuscles, Herbst corpuscles and Merkel disks [78] (Figure 2a). Recent flexible near-sensor system research has been met with the difficulty of integrating individual sensors with these complicated functions. However, research on near-sensor systems with single tactile functions has gradually improved [79]. As a pressure perception system, the four basic pressure perception mechanisms which exist for near-sensor system construction have their own advantages. The piezoresistive mechanism has a simple principle; fundamentally, the resistance of the piezoresistive sensors will be changed along with pressure through a specific function, which is generally negative relevant. Because of their simple structure and wide selection of materials, the preparation and integration of piezoresistive sensor are easy in a large-scale system [80]. The sensor function layer

(SFL) is the material between two electrodes which ensures that the piezoresistive sensors are working properly. A flexible SFL with conductivity can be made of some conductive materials such as graphene, carbon nanotubes or carbon nanofiber [81–83] and combined with flexible organic polymer materials like polydimethylsiloxane (PDMS), thermoplastic polyurethane (TPU) or resin [84–86]. What is more, optimizing the piezoresistive sensors' performance requires a microstructure design [87–89]. Similarly, the design of flexible front-end processing units is also important for implementing near-sensor perception systems. Both neuromorphic devices and logic circuits can filter redundant data from the sensing terminal. Sengupta et al. [90] designed a flexible and stretchable electro-spun carbon nanofiber (CNF) sensor for an intelligent perception system. This sensor has a simple sandwich structure with a PDMS layer by bonding a CNF bundle to copper tape electrodes on two edges and encapsulating them. It will output a voltage of approximately 0–1.2 V in response to a bending angle of 0–90°. This flexible sensor array with a crisscross structure can also be implemented for gesture detection and recognition. A Wheatstone bridge oscillator can generate several numbers of spikes with the voltage output from the sensor (Figure 2b). This mechanism allows pressure and bending signals to be transferred as spikes, and the capacity of the signal will accumulate to reach a threshold and trigger another signal to the back-end units (e.g., Artificial Neural Network). This work testifies to the various gestures involved and allows us to obtain the number of spikes in their curves synchronously. Different curve shapes and diverse gestures are the conditions used for classification. A near-sensor tactile system designed by Liu et al. [91] and Jiang et al. [92], substituting the hardware circuit with a neuromorphic transistor, significantly increased the capabilities of the wearable device. According to this approach, sensors and neuromorphic devices design can become more free, but require more energy consumption and are less wearable. The use of organic material in the preparation of neuromorphic transistors has a better compatibility with near-sensor perception systems compared to hardware circuits (Figure 2c–e). Fang et al. [93] introduced a new perception system with full flexibility, an integrated flexible pressure sensor and a flexible VO<sub>2</sub> insulator-metal transition memristor on a polyethylene naphtholate two formic acid glycol ester (PEN) substrate (Figure 2f). This system needs a minimum pressure input of 3.82 kPa and a frequency output of more than 9.6 kHz. The structure of a capacitive sensor is like that of the piezoresistive sensors. The difference between them is the capacitance and resistance, respectively. What this means is that the functional layer can be prepared using non-conductive materials. Kim et al. [94] designed a capacitive sensor with PDMS + Ag flakes + HA, MIBK or Chloroform sinter-free ink as the electrodes and PDMS as the dielectric layer. The sensor can respond to both pressure and stretching (Figure 2g). It shows an excellent strain-insensitive performance, with only 0.002 of sensitivity per 1% strain at 120% stretching and a pressure sensitivity of 0.64 kPa<sup>−1</sup> ranging from 0 to 1.8 kPa. A flexible Al/TiO<sub>2</sub>/Al memristor was used to construct the near-sensor perception system along with a flexible sensor. The weights trained by the neural network were mapped to the conductance of the memristor array, allowing the system to provide feedback on a specific pressure pattern input.

Piezoelectric and triboelectric sensors can operate without a power supply in contrast to piezoresistive and capacitive sensors [95]. A ceramic material is useful due to the strong piezoelectric effect [96,97]. Jung et al. [98] created a flexible artificial mechanoreceptor inspired by human skin. The HZO/TaN memristor and SiO<sub>2</sub> electric insulation layer as the memory and HZO w/Al<sub>2</sub>O<sub>3</sub> as the sensor were deposited onto a MICA film layer by plasma-enhanced chemical vapor deposition (Figure 2h). This integration of a sensor and front-end processing units onto a single flexible substrate can decrease the size of the perception system and increase its practicality. The sensor exhibits excellent performance in linearity within the range of 2–25 kPa. This system uses a non-volatile memristor as the front-end processing to demonstrate Braille recognition with an accuracy of up to 90.8% which was verified by deep neural network (DNN) software. Similarly, a triboelectric sensor without a power source can electrify through friction. Han et al. [99] designed a triboelectric nanogenerator (TENG) with an Al/PTFE/Al sandwich structure including a

biristor neuron (Figure 2i). When pressure in the range of 3.3~5.3 kPa is applied, a small shift between the Al electrode and polytetrafluoroethylene (PTFE) can produce charges of opposite polarity and current in the circuit. The biristor neuron can output spikes of different frequency with the current generated by TENG. As a result, the TENG–biristor neuron can convert pressure signals into frequency signals, like the tactile receptors in human skin. For MNIST dataset deducing, SNN utility in the back-end unit can achieve an accuracy of 85.8%. Piezoelectric and triboelectric sensors also have a great potential in edge computing due to their self-powering abilities. This system works properly within the circumstances of continuously changing pressure.



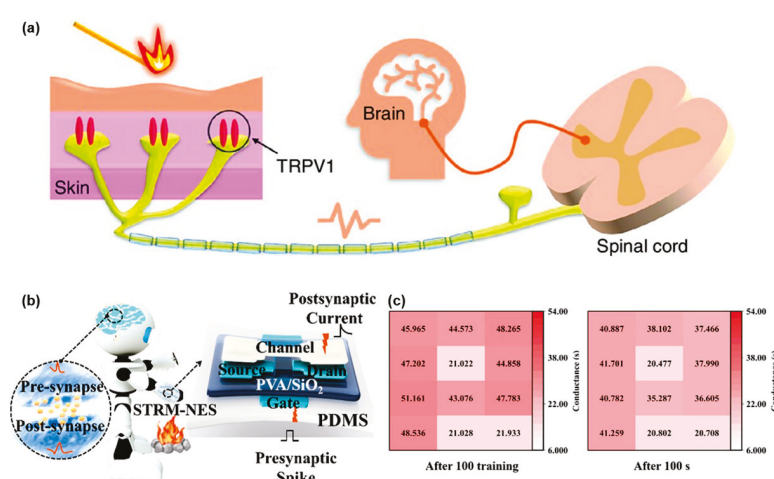
**Figure 2.** Near-sensor tactile system. (a) Neural pathway of tactile system in human beings. Reprinted with permission from Ref. [99]; Copyright 2022 John Wiley and Sons. (b) Schematic image of intelligent glove with Wheatstone bridge oscillators as front-end processing units. Reprinted with permission from Ref. [90]; Copyright 2022 American Chemical Society. (c) Flexible sensors and ion-gate transistor with signal matching circuit. Reprinted with permission from Ref. [91]; Copyright 2023 John Wiley and Sons. (d) Structural diagram of ion-gate transistor. (e) Flexible sensors and transistor array with spike-coding circuit. Reprinted with permission from Ref. [92]; Copyright 2022 John Wiley and Sons. (f) Structural diagram of memristor as front-end processing unit. Reprinted with permission from Ref. [93]; Copyright 2022 Elsevier. (g) Structural diagram of a flexible sensor used in near-sensor system. Reprinted with permission from Ref. [94]; Copyright 2021 John Wiley and Sons. (h) Diagram of flexible near-sensor system prepared using inorganic materials. Scale bar: 100 nm. Reprinted with permission from Ref. [98]; Copyright 2024 John Wiley and Sons. (i) Self-powered near-sensor system and its synaptic characteristics. Reprinted with permission from Ref. [99]; Copyright 2022 John Wiley and Sons.

In conclusion, the feasibility of a near-sensor tactile system has been verified by a number of studies. Compared to a conventional sensor–ADC–backend system structure, the consumption of the near-sensor tactile system reduces 1~2 orders of magnitude due to the redundant data decline [23]. However, a simpler system with one sensor and one neuromorphic device still faces a clear limit in terms of detecting and recognizing pressure

patterns. Therefore, it is necessary to design and construct a stable and uniform flexible near-sensor tactile system array for wearable devices.

### 3.2. Flexible Near-Sensor Thalposis System

The thalposis system is the part of the somatosensory system which allows humans to avoid frostbite and burns (Figure 3a). In contrast to the tactile system, which is used for object surface topography recognition and engages in daily communication, the temperature perception system only allows humans to sense temperature magnitude. Temperature can be measured by calculating the voltage at two ends of a thermistor or the current through it [100,101]. However, researching the neuromorphic temperature perception system is meaningful for electronic skin design for humanoid robots. A temperature sensor can be roughly categorized as either a thermocouple or a thermistor sensor. A thermocouple sensor calculates temperature by detecting the potential difference between two ends of a metal wire, while a thermistor sensor measures temperature according to changes in the thermistor resistance layer. Both thermocouple sensors and thermistor sensors are used in the sensing units of near-sensor thalposis systems with their own advantages, respectively. Compared to a thermocouple sensor, a thermistor sensor has a higher accuracy and a smaller size, making it capable of detecting slight temperature changes accurately and integrating easily. However, their linearity is not good. Flexible temperature sensors are typically prepared using carbon series materials (such as CNTs, rGO and graphite) and semiconductor films with high temperature coefficients (such as  $\text{MoS}_2$ , MCNO and  $\text{Ag}_2\text{S}$ ) due to their compatibility with flexible organic polymers [102–107]. Thermistor sensors are often used in near-sensor systems because their thermal resistance mechanism and the electrical signal input requirements of their front-end processing units are well studied. Wang et al. [108] introduced a self-healing multimodal electronic skin for deformation and temperature perception. This system has a three-terminal transistor structure with a carbon nanotube (CNT) channel and CNT electrodes. The semi-conducted part and the metallic part are isolated by PVA/ $\text{SiO}_2$  (Figure 3b) and its temperature detection ranges from 20 °C to 50 °C. Similar to living skin, this system can break down in an environment with a temperature higher than 50 °C. Yet the dispersed PVA chain will cross-link; in other words, it can return back to its normal condition after the temperature returns to below 50 °C. Different temperatures can result in varying drain currents from the transistor. The temperature of the ambient environment affects the conductivity of the transistor array, and the distribution of temperatures can be directly reflected by the distribution of conductivity (Figure 3c).



**Figure 3.** Near-sensor thalposis system. (a) Neural pathway of thalposis system in human beings. Reprinted with permission from Ref. [101]; Copyright 2022 John Wiley and Sons. (b) Diagram of stretchable temperature-responsive multimodal neuromorphic electronic skin (STRM-NES). (c) Conductance of the device after training with a letter “P” shaped heat source and its conductance after 100 s. Reprinted with permission from Ref. [108]; Copyright 2022 American Chemical Society.



Current research on near-sensor thalposis systems is still in its primary stages. They are only used to help increase the accuracy of pressure pattern recognition in tactile receptors. However, a high-performance pressure sensor array with a neural network would be better than bioreceptors. Therefore, research into temperature pattern recognition is no longer an urgent priority. However, the near/in-sensor architecture and neuromorphic device offer more unique advantages in classification and recognition. Therefore, thalposis system research should mainly concentrate on preparing large-scale arrays.

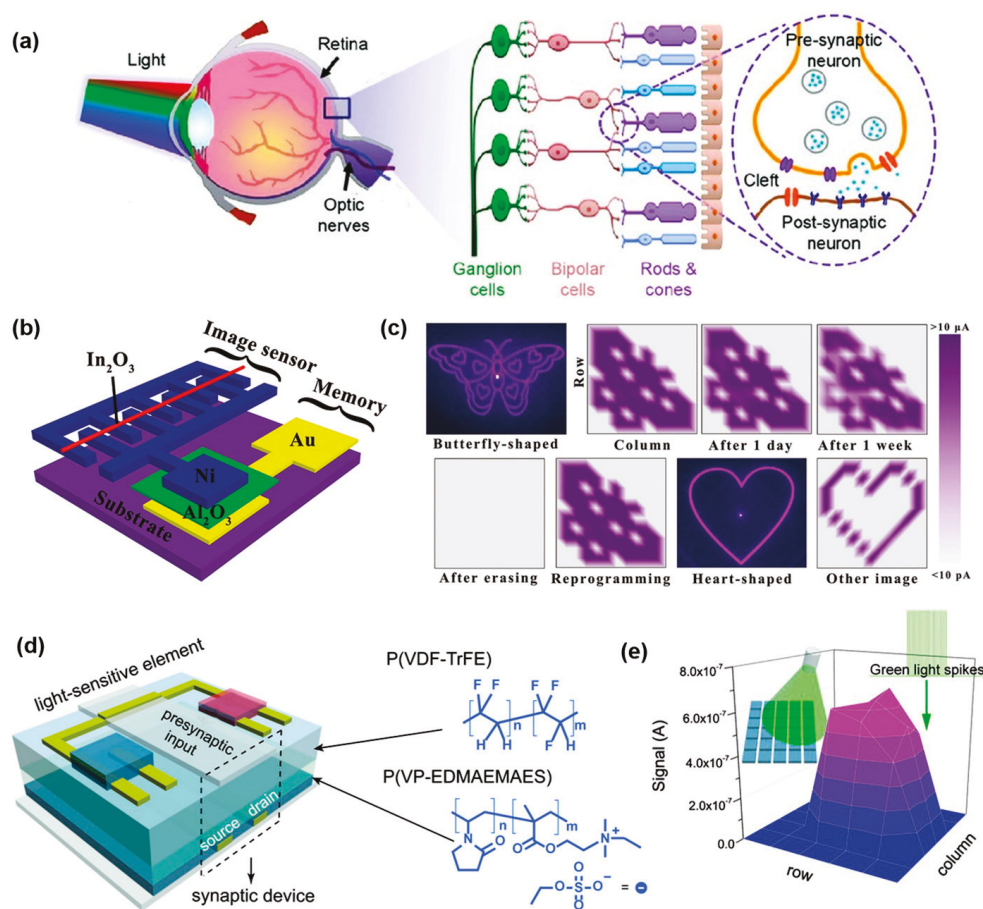
### 3.3. Flexible Near-Sensor Visual System

The visual system allows humans to locate objects and recognize visual information. It is composed of photoreceptors, a visual pathway and a visual center (Figure 4a) [109]. Capturing visual information (i.e., optical signals) and converting neural signal photoreceptors helps the visual center to make judgements and respond in time. Additionally, the visual system can enhance the recognition accuracy of other perception systems. A near-sensor visual system inspired by the human visual system would have the characteristics of a low power consumption and a robust information processing ability [110–112]. Thanks to the present technology, a flexible light-sensitive unit for artificial visual systems can be prepared easily. However, designing a near/in-sensor visual system is complex because of the requirements of capturing moving objects and accurately recognizing images. Therefore, the near/in-sensor visual system design focuses on the front-end processing units and back-end units.

The working mechanism of a photosensor is based on the photoelectric effect or photoconductivity of the semiconductor material. Valency electrons in PN junctions absorb photons and transit them into the conduction band with light illumination. This will produce free electrons and holes. In this way, an optical signal can be converted into an electrical signal. Semiconductor materials such as silicon, indium oxide, and carbon series materials combined with flexible organic polymers are used to prepare flexible photosensors [113–118]. To improve flexibility, rigid materials are shaped into nano size, such as nanotubes, nanorods and nanowires [119,120]. A strong information processing capability is required for both the front-end units and back-end units. Here, both neuromorphic devices and convolution neural networks (CNNs) are used to recognize optical images input from photosensors accurately. Chen et al. [121] designed a flexible printing platform integrated with a Ni/In<sub>2</sub>O<sub>3</sub> semiconductor micrometer-size wires (SMWs)/Ni photosensor and a Ni/Al<sub>2</sub>O<sub>3</sub>/Au nonvolatile memristor on it (Figure 4b). The resistance of the photosensor can switch between a high resistance state and low resistance state under modulating UV light as low as 0.528 mW/cm<sup>2</sup>. As the photosensor and memristor are connected in parallel, a large enough voltage in the memristor can switch it from the OFF state to the ON state and maintain its state after turning off the power. Furthermore, a large-scale array was developed to identify butterfly and heart-shaped patterns. Inputs of different shapes can be easily distinguished by measuring the current output from the memristor (Figure 4c). Wang et al. [122] integrated a fully organic flexible visual system with an organic heterojunction as a photosensor and an organic synaptic transistor. This system can detect incident light at a wavelength of 850 nm and wavelength of 0.08 mW/cm<sup>2</sup>. The intensity and irradiated area of the incident light can be visualized by a simple readout of the post-synaptic current (PSC) (Figure 4d,e).

Research on artificial visual systems has focused on the in-sensor system benefits of novel materials discovered to have both light-sensitive and brain-like properties. The in-sensor visual system has a smaller size but larger scale integration capability compared to the near-sensor visual system. Section 4.2 will provide a detailed review of the in-sensor visual system.



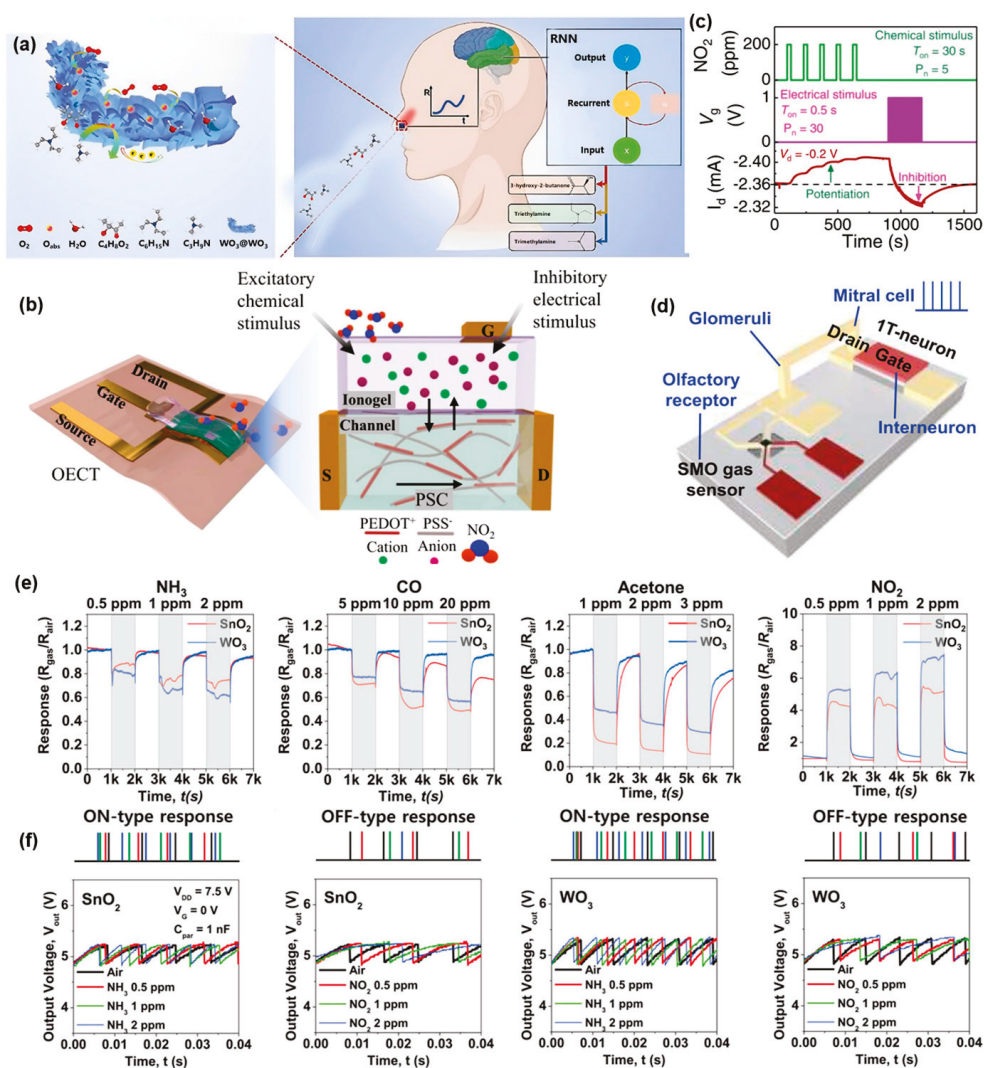


**Figure 4.** Near-sensor visual system. (a) Neural pathway of visual system in human beings. Reprinted with permission from Ref. [109]; Copyright 2020 John Wiley and Sons. (b) Structural diagram of the image sensor integrated with memristor as front-end processing unit. (c) Devices after modulated by butterfly-shaped and heart-shaped ultra-violet light source and its PSC accordingly. Reprinted with permission from Ref. [121]; Copyright 2018 John Wiley and Sons. (d) Structural diagram of the light-triggered organic neuromorphic device (LOND). (e) Devices triggered by green light spikes and display the illumination region through PSC. Reprinted with permission from Ref. [122]; Copyright 2018 John Wiley and Sons.

### 3.4. Flexible Near-Sensor Olfactory System

The olfactory system helps us to cognize specific objects from their unique scent. Essentially, this system needs to distinguish various molecules and respond accordingly for a proper working condition [123,124]. An olfactory sensor which is inspired by the human olfactory system and based on chemical sensing principle can detect the concentration and type of various molecules through chemically reactions (Figure 5a). To some extent, the design of a flexible sensor depends on the molecules to be detected. For instance, a PDMS/Ppy double layer nanostructure, which is used to detect organic molecules through its triboelectric/gas-sensing coupling effect, can detect acetone concentrations as low as 100 ppm [125]. Similarly, single-walled carbon nanotubes (SWCNTs) combined with olfactory receptor-derived peptides (ORPs) are useful for detecting harmful concentrations of trimethylamine (TMA) with a lower limit of 0.01 ppq [126]. Through the chemical reaction, chemical molecules can transform information into electric signal [127]. Instead of inorganic material, organic material is more prevalent in olfactory sensors due to their greater variety of chemical bonds. Chouhdry et al. [128] designed an organic electrochemical transistor (OECT) with a PEDOT:PSS channel, a poly(ethylene glycol) diacrylate (PEGDA) monomer and a 1-hydroxycyclohexyl phenyl ketone photo initiator as the chemoreceptive

material, as well as a gate electrolyte layer. An ion gel made of [EMIM][TSFI] was produced as a gas sensing layer, connected to the gate of the OCET (Figure 5b). This near-sensor olfactory system can detect  $\text{NO}_2$  concentrations starting from 2.66 ppm. Its output exhibits long-term potentiation and depression effects (Figure 5c). Han et al. [129] designed a type of semiconductor metal oxide gas sensor with  $\text{SnO}_2$  and  $\text{WO}_3$ , respectively, and a neuron integrated into it with traditional metal oxide semiconductor field effect transistor (MOSFET) chips (Figure 5d). Gas sensors can capture specific gas concentrations with a lower limit of 0.5 ppm via resistance changing and a loop current (Figure 5e). This loop current determines the output frequency from the 1T-neuron. The output of gas sensors made from  $\text{SnO}_2$  or  $\text{WO}_3$  can be another input of a neural network for gas recognition and classification (Figure 5f).



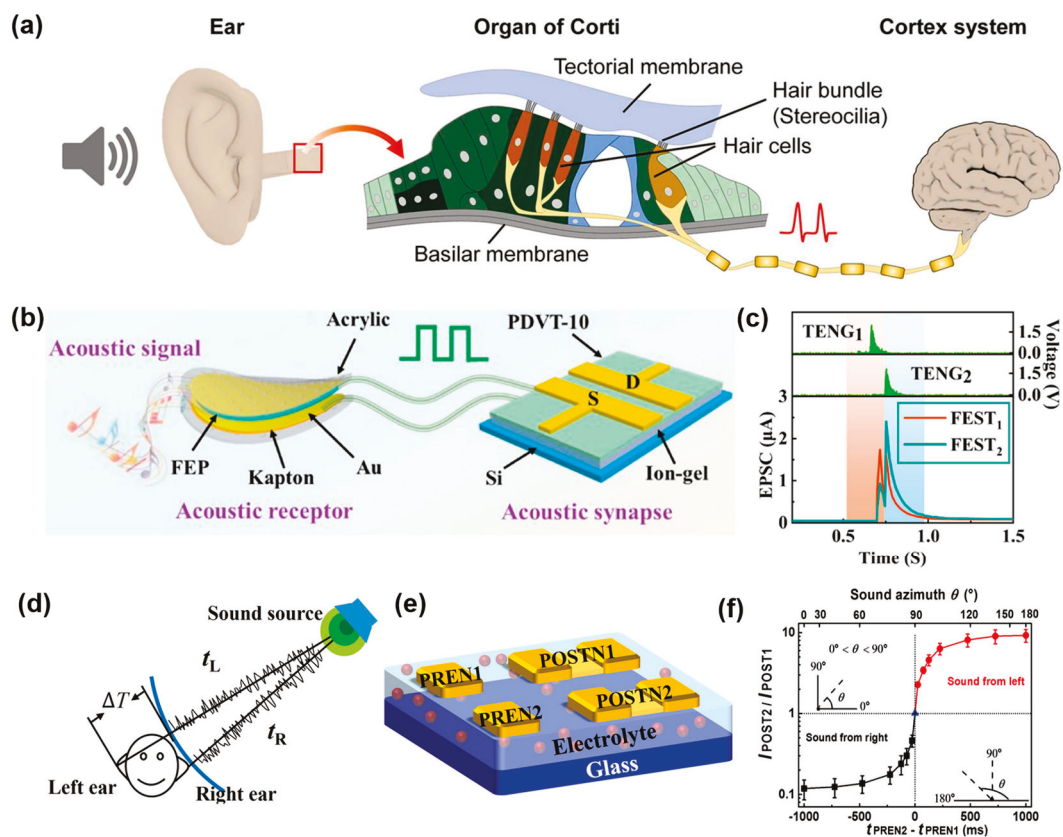
**Figure 5.** Near-sensor olfactory system. (a) Neural pathway of olfactory system in human beings. Reprinted with permission from Ref. [127]; Copyright 2024 John Wiley and Sons. (b) Structural diagram of the  $\text{NO}_2$  sensitive organic electrochemical transistor (OEET). (c) Electrical characteristics of OEET modulated by 200 ppm  $\text{NO}_2$  concentration and gate voltage. Reprinted with permission from Ref. [128]; Copyright 2023 Springer Nature. (d) Structural diagram of the SMO gas sensor integrated with transistor neuron. (e) Current response of  $\text{SnO}_2$  and  $\text{WO}_3$  gas sensor under same gas stimuli. (f) Frequency response of the device under same gas stimuli. Reprinted with permission from Ref. [129]; Copyright 2022 John Wiley and Sons.

The combination of a near-sensor olfactory system and a flexible device as a more intelligent molecular detector has occupied a key seat in current research on harmful gases detection. Flexible gas sensors have a ultra-high quality of detection sensitivity compared to the biological olfactory system, particularly a lower measurable threshold. However, due to the material utility of a gas sensor, only a few gas molecules can be detected through chemical reactions in the sensitive layer. Thus, expanding the range of detectable molecules and designing the back-end unit for molecule classes distinction are still challenges we are currently facing.

### 3.5. Flexible Near-Sensor Auditory System

The biological auditory system enables humans and other species to locate the source of sound and identify meaningful information (Figure 6a). Similarly, the artificial auditory system can locate a sound source through binaural effects and identify acoustic information by perceiving frequency and amplitude [130–132]. Indeed, the auditory sensor converts frequency and amplitude signals into electrical signals for the front-end processing units. For flexible auditory sensors in a near-sensor auditory system, a low detection limit is necessary to detect the small mechanical vibrations caused by sound waves [133,134]. An electromagnetic material is a typical component of an auditory sensor with a high sensitivity and fast response. Additionally, high-sensitivity pressure sensor can be used as auditory sensors due to their ability to detect of micro vibrations [135–138]. Liu et al. [139] designed a triboelectric nanogenerator (TENG) with an Au/fluorinated ethylene propylene (FEP) film/Kapton film for acoustic signal detection. Furthermore, they developed a synaptic transistor with a PVDT-10 channel and an [LI][TSFI] ion gel dielectric layer (Figure 6b) to capture and accumulate waves in the frequency range of 50–5000 Hz. The TENG can output a voltage of 126 mV/dB. Two TENGs and two field effect synaptic transistors (FESTs) are used to locate and determine the orientation of a sound source by calculating the amplitude ratio of two FESTs (Figure 6c). The FEST can also accurately detect and filter acoustic signals in noisy environments during processing. He et al. [140] designed a multi-gate synaptic transistor with an IGZO channel and a chitosan solid electrolyte film. This transistor can simulate the binaural effects of the human auditory system (Figure 6d,e). Like the disparate position of a human's two ears, auditory sensor will receive the signals with different strengths according to their position. The distance between the sensors and the sound source can be measured by measuring the postsynaptic current (PSC) produced from audio signals. The approximate position of the sound source can be obtained by calculating the amplitude ratio of the PSC in a synaptic transistor (Figure 6f).

Differently to other systems, research on the artificial auditory system is relatively complete, including as the creation of a flexible device, hardware system and circuit match. Thanks to significant advances in artificial intelligence, the characteristics of acoustic signals extracted by neuromorphic devices can be accurately recognized by a neural network. A higher compatibility of all of the parts in a near/in-sensor system is needed for a wearable intelligent system which is integrated with a perception system.



**Figure 6.** Near-sensor auditory system. (a) Neural pathway of olfactory system in human beings. Reprinted with permission from Ref. [135]; Copyright 2023 Elsevier. (b) Structural diagram of the acoustic sensor connected with synaptic transistor. (c) PSC current of FEST<sub>1</sub> and FEST<sub>2</sub> when the sound comes from the right direction. Reprinted with permission from Ref. [139]; Copyright 2020 Elsevier. (d) Schematic image of the binaural effect. (e) Structural diagram of dual-gate synaptic transistor. (f) Function of the sound source azimuth estimation by calculating the ratio of the PSC of two transistors. Reprinted with permission from Ref. [140]; Copyright 2019 John Wiley and Sons.

#### 4. Flexible In-Sensor Artificial System

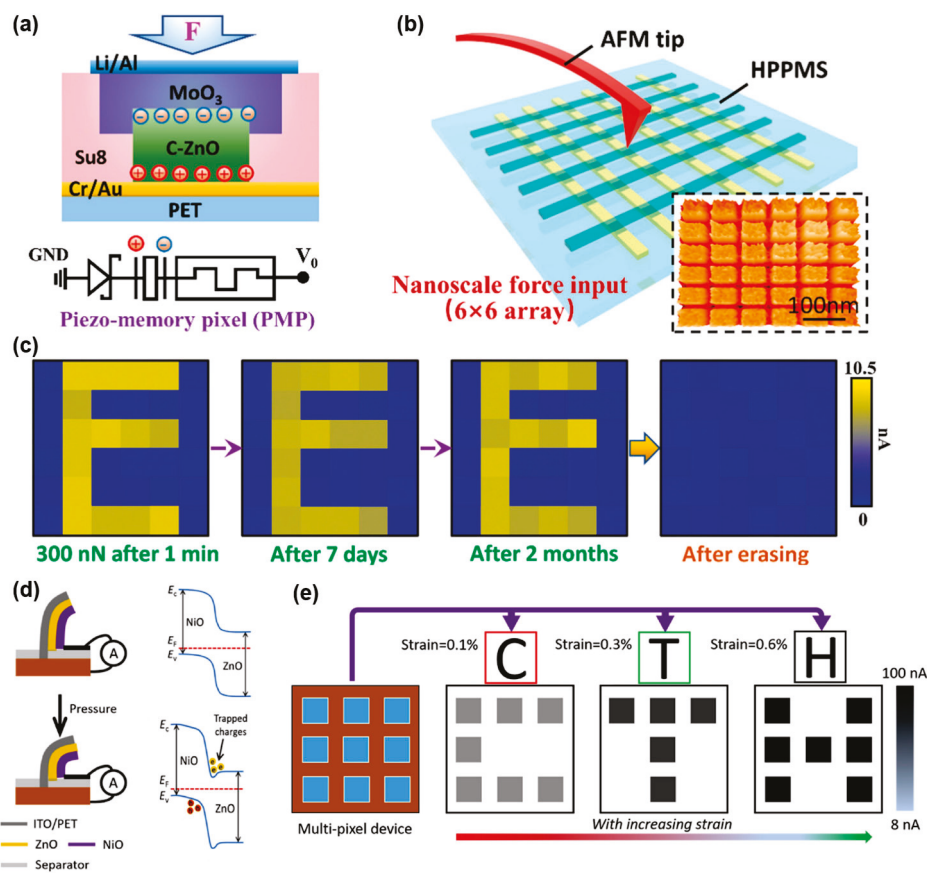
On the basis of a near-sensor artificial system, the front-end processing unit and sensing unit need to be integrated into in-sensor systems further and entirely. In-sensor computing architecture is smaller and consumes less power than near-sensor computing architecture [141,142]. Sensors that combine sensing, storing and computing functions or sensing and computing functions are referred to as multi-functional sensing units. The in-sensor computing architecture eliminates the redundant data between the sensing and computing units by data pre-processing in the former part [21]. Implementing powerful features into in-sensor artificial systems, such as material selecting and device structure designing, is still a challenge in this field despite their considerable advantages. Replacing electro-resistive materials with other sensing signal-induced resistive materials is a relatively good design solution for the introduction of a novel material to neuromorphic devices. Combining sensors and neuromorphic devices into a unified entity as a new integrated structure is another solution.

##### 4.1. Flexible In-Sensor Tactile System

For an in-sensor tactile system, materials with both stress-response and synaptic characteristics have not yet been proposed. Therefore, integrating pressure-sensitive materials and resistive materials into a single device and designing a rational structure has become the main course of action [143,144]. Jiang et al. [145] designed a flexible multi-functional sensing unit for a complex structure with a PET substrate, Cr/Au bottom



electrode, Su8/C-ZnO/Su8 pressure sensitive layer, MoO<sub>3</sub> resistive layer and Li/Al upper electrode (Figure 7a). In addition, ZnO nanowire is a common piezoelectric material used for self-power supply instantiation. It can generate a voltage of 0–5 V under a pressure of 0–400 nN. A  $6 \times 6$  piezo memory pixel (PMP) array (Figure 7b) is used to store English letters with considerable durability (Figure 7c). What is more, Kumar et al. [146] designed a PET/ITO/ZnO/NiO flexible film inspired by the mechanoreceptor in human skin. Because of the difference in electron affinity between ZnO and NiO, charges can be trapped in NiO under the pressure, which is similar to the P-N junction. Through this mechanism, the conductance of the device can be modulated by applied pressure (Figure 7d). Specifically, the same number of spikes can generate different currents with different pressures. Additionally, a  $3 \times 3$  array can store English letters. The PSC of the device can be modulated by pressure and strain (Figure 7e). To improve the performance of in-sensor tactile system, a new mechanism for easily preparing materials and integrating multi-functional sensing units is necessary.



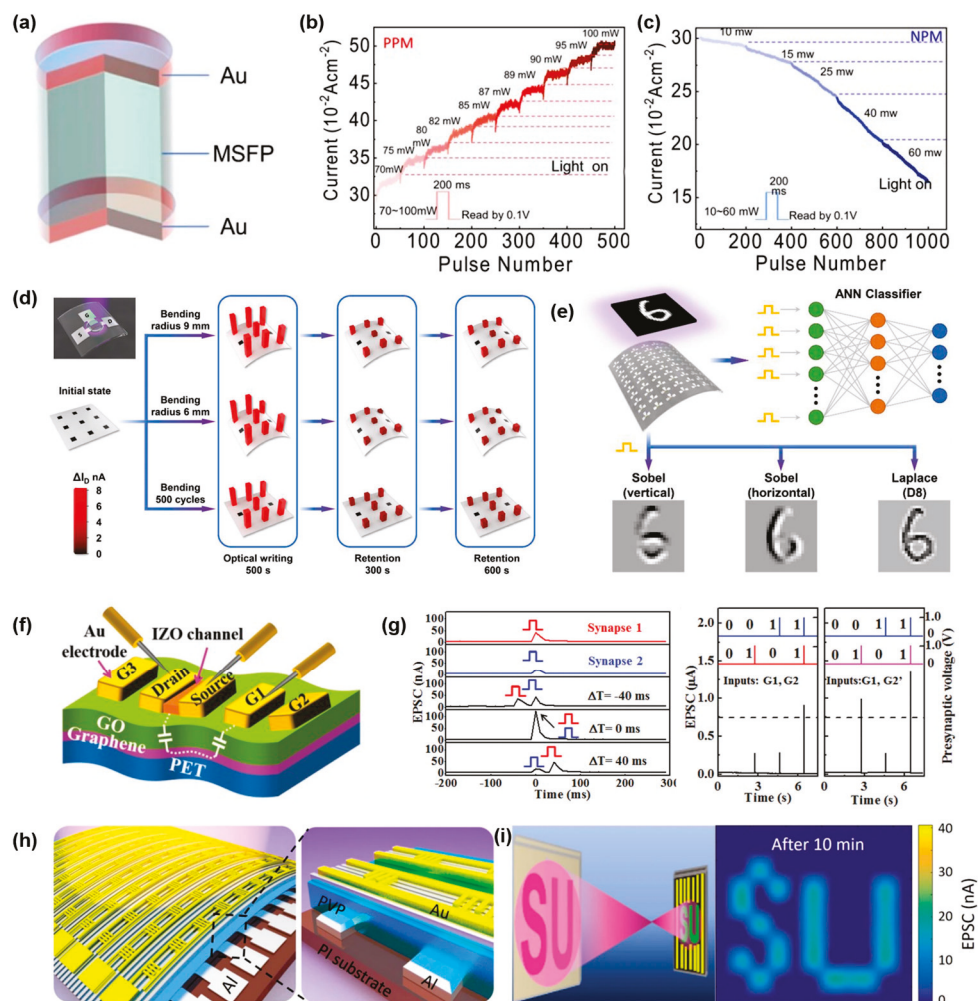
**Figure 7.** In-sensor tactile system. (a) Schematic image of the PMP. (b) AFM image and diagram of the  $6 \times 6$  array. (c) Pressure signal perception and storage characteristic. Reprinted with permission from Ref. [146]; Copyright 2021 Elsevier. (d) Schematic image of the in-sensor system inspired by the fine hair on the human body. (e) Response of letter “C”, “T”, “H”-shaped pressure inputs under different strain. Reprinted with permission from Ref. [147]; Copyright 2020 Elsevier.

#### 4.2. Flexible In-Sensor Visual System

Compared to the near-sensor visual system, the in-sensor visual system has been systematically researched due to the proposal of a wide variety of photo-induced resistive materials [147–152]. This means that neuromorphic devices can be modulated by an optical spike being directly dropped into the procedure of electric spike converting. Integrating a single multi-function sensing unit with two functional units (a sensor and a transistor) is beneficial for a further large-scale integration. Zhou et al. [153] designed an Au/modified



silk fibroin protein (MSFP)/Au resistive random-access memory (RRAM) with a simple sandwich structure (Figure 8a). The resistance of the device can be transferred from HRS to LRS with a light intensity with a power of greater than 60 mW, and can be transferred to HRS from LRS with a power less than 60 mW (Figure 8b,c). Hardware contrast enhancement and background denoising can be implemented via these features. Li et al. [154] designed a flexible VO<sub>2</sub>/mica film with Pt electrodes for crossbar array preparation. This VO<sub>2</sub>-based light-modulated memristor exhibits good bending stability and a long retention time for the conductance state (Figure 8d). Furthermore, this device can be modulated by visible light with an intensity of greater than 1 mW/cm<sup>2</sup>. Combining the memristor array and artificial neural network (ANN) classifier demonstrates the system's powerful intelligence in MNIST dataset recognition and motion detection (Figure 8e). Wan et al. [155] designed a multi-gate flexible neuromorphic transistor with a PET/graphene/GO/Au layered structure (Figure 8f). A device with an IZO film as a channel can output different PSCs based on the distance between the channel and gate. By setting reasonable thresholds or changing the position of the gate, different basic logic functions such as AND, OR or XOR can be realized (Figure 8g). Deng et al. [156] designed a Dif-TES-ADT crystal material with the light response characteristic. It was combined with a PVP dielectric layer, Al gate and a Au electrode for manufacture of photo synaptic device (Figure 8h). This device can accumulate light spikes with an incident light intensity ranging from 0.001 to 53 μW/cm<sup>2</sup>. Additionally, they prepared a large-scale array for long-term storage of input optical images (Figure 8i).



**Figure 8.** In-sensor visual system. (a) Structural diagram of the Au/MSFP/Au light sensor. (b,c) Optical modulation characteristics of the device; positive and negative effects are bounded by 60 mW.

Reprinted with permission from Ref. [153]; Copyright 2023 Springer Nature. (d) Data storage capability of the  $3 \times 3$  array with good bending stability. (e) ANN is used as the back end to classify MNIST dataset. Reprinted with permission from Ref. [154]; Copyright 2022 John Wiley and Sons. (f) Structural diagram of the multi-gate transistor. (g) Implementation of AND/OR logic function by multi-gate modulation. Reprinted with permission from Ref. [155]; Copyright 2016 John Wiley and Sons. (h) Structural diagram of a large-scale photo synaptic device array. (i) Storage capability of the photo synaptic device array. Reprinted with permission from Ref. [156]; Copyright 2019 Springer Nature.

Currently, flexible photo-induced resistive materials and circuit designs for in-sensor visual systems have extended, resulting in significant progress. However, the biological visual system has more powerful and complex functions than the function-specific artificial visual system. Furthermore, integrating the visual system with other compatible artificial sensory systems is still a challenging next step.

## 5. Summary and Outlook

The near/in-sensor computing paradigm is an emerging solution for real-time and data-intensive applications. Processing data directly at the sensor terminal significantly improves the area, time and energy efficiency of hardware. Inspired by the brain, low-level processing such as filtering and denoising can be implemented by neuromorphic devices at the sensor terminal. For the IoT, the near/in-sensor computing architecture is the best choice for wearable application due to its real-time capability and low power consumption. The sensing units and front-end units in near-sensor architecture can be designed separately because of their physical separateness. Therefore, materials such as inorganic films and organic semiconductors can be used for flexible device fabrication. For in-sensor architecture, selecting the flexible material carefully is beneficial for entirely integrating the sensor and the neuromorphic device. Although near/in-sensor systems show great potential in practical applications, most devices are still in an early stage of development. Because of their limited functionality, current near/in-sensor systems can only be used in specific scenarios. Near/in-sensor computing involves multiple disciplines such as materials, circuits and algorithms. The back end is an important part in the design of wearable smart devices. To fully realize a near/in-sensor computing system, all parts of the system must be simultaneously optimized. From near-sensor architecture to in-sensor architecture, to implement high-level processing at the sensor terminal, continuous optimization of the material, device and circuit design is required. This will allow for autonomous monitoring and the analysis of physiological signals without relying on cloud-based resources and will also make implementing wearable devices with a lower power consumption and greater intelligence possible.

From the perspective of developing high performance wearable devices, replacing traditional computing architecture with low-power near/in-sensor computing architecture is extremely possible. The emerging neuromorphic devices have the possibility of realizing near/in-sensor perception systems, but it is hard to achieve an operational stability equivalent to that of MOSFETs. Therefore, devices with a ferroelectric mechanism or three terminals are often used to improve the stability of the system. The design of an in-sensor system is more difficult and complex than that of a near-sensor system. What this means is that more ground-breaking designs with novel structure and mechanism of device are required. Meanwhile, the additional requirement of the design of flexible material is also a problem that needs solving. Because of the advantages of portability and low energy consumption, from the perspective of application and the market, wearable devices with a flexible near/in-sensor system are likely to squeeze the market space of traditional artificial intelligence devices in future market competitions. Due to their portability and user experience, traditional wearable devices have gained a significant market share from rigid device. However, the increasing functionality of these devices means that it takes a higher power consumption to impair the battery life. Furthermore, more generated data need to

be uploaded for cloud processing. Traditional wearable devices meet more difficulty in current market environment with these increasing drawbacks. Creating flexible near/in-sensor systems, with an in situ information processing ability, further reduces the power consumption and data transfer latency. These advantages help them to hold the trophy in the wearable device market and make them eligible to compete with AI-based devices. Although traditional architecture combined with ANN is popular in current wearable smart devices, we strongly believe that the next generation of wearable intelligent devices will greatly benefit from the integration of near/in-sensor computing architecture and neuromorphic devices.

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## Abbreviations

|        |                                                   |
|--------|---------------------------------------------------|
| IoT    | Internet of Things                                |
| ADC    | Analog-to-Digital Converter                       |
| SFL    | Sensor Function Layer                             |
| DNN    | Deep Neural Network                               |
| TENG   | Triboelectric Nanogenerator                       |
| CNN    | Convolutional Neural Network                      |
| PSC    | Postsynaptic Current                              |
| ANN    | Artificial Neural Network                         |
| MOSFET | Metal Oxide Semiconductor Field Effect Transistor |

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