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Review article

Hydrogel-based Biosensors in Biomedical Applications

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Abstract. Hydrogels have great potential for applications due to their high water content and unique 3D interconnected structure. Due to their excellent biocompatibility, tunable dynamic characteristics, and sensitive responses to environmental stimuli, including temperature, pH, and ions, hydrogels are an ideal material platform for new biosensors. While synthetic hydrogels can achieve precise control of structure and function through chemical or physical methods to meet the needs of various applications, hydrogel has the advantages of abundant resources and green environmental protection. Wearable medical devices have advanced significantly. The electrochemistry of anti-pollution hydrogels or optical transmission platforms can be used to detect high-level tumor markers, and the functionalization of conductive hydrogels can lead to new methods for heart tissue engineering and nerve repair. The most recent developments in sensor design, material selection, and manufacturing techniques were overviewed, along with their potential applications across various domains and the challenges that remain in achieving stability, sensitivity, and clinical translation.

Keywords: Hydrogels, biosensors, 3D interconnected structure, biocompatibility of biosensors, tissue engineering.

1. INTRODUCTION

A biosensor is generally defined as an analytical device that converts a biological response into a measurable and processable signal, serving as the bridge between biochemical reactivity and technology [1]. Biosensors are attracting the attention of many researchers for their astonishingly practical applications in the pharmaceutical, clinical, biomedical, and healthcare sectors. These are now being used successfully to identify, eliminate, and treat diseases, after being used before

to find bacteria, pathogens, and viruses. Also, these sensors can detect chemicals without drawing blood. It also reduces the need for hospital stays to monitor body chemistry, giving us access to information about the chemicals in our bodies from anywhere [2-3]. Biosensors can be used with a wide range of samples, including body fluids, food samples, cell cultures, and environmental samples. [4]

Hydrogel is a three-dimensional cross-linked polymer. It is very elastic, stable, and can absorb and hold water. It can soak up hundreds of times its weight in water. These properties further contribute to the efficiency of biosensing. The pore size and the hydrogel's swelling rate determine the diffusion constant for biomolecules and, to a greater extent, the sensor's response time. The high degree of biomolecule immobilization increases sensitivity and detection limits, as pore size and surface chemistry can be adjusted. Compared with traditional rigid sensor materials, the high elasticity and water-rich properties of hydrogels more closely resemble those of natural tissues, thereby improving biocompatibility and reducing inflammatory responses. In addition to being passive matrices, hydrogels can be identified as active facilitators of highly responsive, selective, and biocompatible biosensing systems by explicitly coupling these material properties to biosensor performance metrics. Swelling disrupts the molecular chain structure, weakens material properties, accelerates degradation, and thus reduces its application value. Hydrogels, on the other hand, can respond to a variety of stimuli, making them ideal for sensing applications [5]. Hydrogels are much better than regular materials for biosensors. Biocompatibility, inflammation, and lack of flexibility are common problems with traditional metals, electrodes, and solid high-molecular materials. Hydrogel is more like natural tissue because it contains a lot of water and can bend. This makes it much less responsive to the environment and more sensitive. Also, hydrogels are easy to control and respond well to their environment, allowing them to remain stable across a wide range of physiological conditions. This makes them a great candidate for a new type of biosensor. A signal transduction pathway that converts the hydrogel response into a measurable signal enables this [6]. A variety of synthetic polymers, such as polyethylene glycol (PEG), poly(N-isopropyl acrylamide) (PNIPAAm), poly(2-hydroxyethyl methacrylate) (PHEMA), and natural polymers, such as chitosan, alginate, dextran, and hyaluronic acid, have been used to make hydrogels for biosensing. Because they are hygroscopic, proteins and cells can't stick to them. Their unique traits, such as biocompatibility, shape-changing ability, and controllable mechanical and chemical properties, make them useful as biosensors [7]. Photothermal therapy (PTT) typically necessitates sustaining tumor lesions at temperatures exceeding 50°C, potentially resulting in localized inflammation and tumor metastasis. To prevent these adverse effects, it is essential to achieve practical anti-tumor efficacy at relatively low temperatures (42-45°C) during PTT treatment. Ding et al. [8] developed a polydopamine (PDA)-coated nucleic acid nanogel for use as a therapeutic complex for siRNA-mediated low-temperature PTT. Lee et al. [9] described the biomedical applications of alginate-based hydrogels for their biocompatibility, adjustable biological behavior, and resemblance to extracellular matrices. Alginate consists of M and G units that can be cross-linked with divalent cations, such as Ca^{2+}, to form hydrogels. Covalent and light-induced (photon-to-cross-linking) approaches leverage increased stability to enable function. With their high water content, porosity, and mechanical flexibility, alginate hydrogels have proven useful matrices for the encapsulation of biologics or cells.

This review provides an overview of recent progress and key findings on hydrogel-based biosensors for bio relevant applications (diagnosis, drug delivery, tissue repair and regeneration, wound healing, etc.). This review presents different types of hydrogel materials for biosensors (natural polymers, synthetic polymers, and conductive materials). It discusses the technical limitations encountered during the development, fabrication, and application of hydrogel-based

biosensors. Furthermore, this article discusses different types of hydrogel materials used to prepare biosensors, including natural polymers, synthetic polymers, and conductive materials.

2. HYDROGEL-BASED BIOSENSORS

Hydrogels are widely used in biosensors due to their high water content capacity, biocompatibility, and ability to respond to environmental changes. Hydrogels can be used as biosensor matrices to immobilize transducers, biomolecules, or responsive components. Biosensors' three primary types of hydrogels are synthetic, natural, and hybrid/composite. The application of hydrogel polymer in biosensing technology with origins is shown in **Table 1 [9-42], Table 2 [43-79], and Table 3 [80-118]**. In this study, as shown in **Table 4**, the advantages and disadvantages of natural hydrogels, synthetic hydrogels, and composite/hybrid hydrogels in biosensors are compared, and their key characteristics in biomedical applications are summarized.

Table 1: Natural hydrogels used in biosensors

Name	Properties	Applications in biosensing
Alginate	Biocompatibility, ease of gelation, and retaining ability. [9]	• Electrochemiluminescence (ECL) based biosensor. [10] • For the early detection of liver cancer using a biosensor encapsulated in an alginate polymer film thin layer. [11] • Encapsulating Zinc Phthalocyanine Dye-Sensitized Photoelectrochemical Biosensor for Hg^{2+} detection. [12] • Alginate membranes that can be electrodeposited for enzyme-based sensors. [13]
Chitosan	Antibacterial effect, biocompatibility, biodegradability, non-toxicity, and high humidity absorption. [14]	• Biosensors that use electricity and chitosan to spot lung cancer. [15] • Sensors made with chitosan and nano-composite-based biological particles to find signs of disease early and detect biomarkers. [16] • A device that uses chitosan-covered ZnS quantum dots to sense heavy metal ions. [17]
Agarose	Reversible thermo-gelling behavior, high biocompatibility, structural modularity, and biodegradability. [18]	• In an immobilization matrix model for a microbial biosensor. [19] • Development of a microfluidics biosensor. [20] • Electrochemical biosensor for catechol. [21] • Reagentless colorimetric biosensing platform. [22]
Gelatin	Water retention, controllable porosity, soft mechanical	• As a Matrix for immobilized biorecognition material. [24] • In electrochemical DNA biosensing. [25] • In a surface plasmon resonance-based biosensor. [26]

	strength, and stimulus responsiveness. [23]	• In preparation for the urea biosensor. [27]
Pectin	Biodegradability, easy gelling ability, and simple control of pectin-based biomaterial. [28]	• In an optical biosensor with immobilized lipase enzymes. [29] • In an amperometric glucose biosensor. [30] • In biosensing detection of hemoglobin. [31] • An optical pH sensor for fish freshness monitoring. [32]
Hyaluronic Acid	Biodegradability, biocompatibility, nontoxicity, and non-immunogenicity. [33]	• High-performance supercapacitor and antifouling biosensor. [34] • In dual-responsive electrochemical biosensors. [35] • In sensitive non-enzymatic glucose sensor. [36] • In sensitive hyaluronidase biosensor based on target-responsive hydrogel. [37]
Dextran	Antifouling abilities, high water retention, and flexible structure. [38]	• In fluorescence-based glucose biosensors. [39] • In prostate-specific antigen biosensors. [40] • In optical biosensor applications. [41] • SPRi sensor for small-molecule drug detection. [42]

Table 2: Synthetic hydrogels used in biosensors.

Name	Properties	Applications in biosensing
Polyethylene Glycol (PEG)	Biocompatibility, high hydrophilicity. [43]	• Microfabricated protein-containing poly(ethylene glycol) hydrogel arrays for biosensing. [44] • As biosensor coatings for the detection of collagenase. [45] • In Fluorescence-Based Glucose Biosensor. [46] • In the development of electrochemical biosensors. [47]
Polyacrylamide (PAM)	Water solubility, high sensitivity, compression strength, and easy fabrication. [48-49]	• An amperometric biosensor based on human cytochrome. [50] • In recyclability for sensitive and colorimetric detection of penicillin G. [51] • In an electrochemical aptasensor for the detection of Aflatoxin B2. [52] • An enzymatic electrochemical biosensor for urea. [53]
Polyvinyl Alcohol (PVA)	Flexibility, biocompatibility, adhesion, self-	• In multifunctional self-healing biosensors. [55] • As wearable biosensors in sweat detection. [56] • In a novel electrochemical biosensor for sensitive detection of glucose. [57]

	healing, and frost resistance. [54]	• In the ultrasensitive detection of folic acid by fluorescence quenching. [58]
Poly(2-hydroxyethyl methacrylate) (pHEMA)	Biocompatibility, softness, and transparency. [59]	• In wearable contact lens biosensing. [60] • In a quartz crystal microbalance sensor. [61] • In improving the biocompatibility of biosensors. [62] • In the construction of clinically important biosensors. [63]
Poly(N-isopropylacrylamide) (PNIPAM)	Stimulus responsiveness, solar water evaporation. [64]	• Microgel-based optical devices for sensing and biosensing. [65] • Temperature sensor applications. [66] • Highly efficient and recyclable catalysts for biosensing. [67] • Electrochemical temperature-controlled switch for a nonenzymatic biosensor. [68]
Poly(methacrylic acid) (PMAA)	Biocompatibility, pH-Responsiveness, and mechanical properties. [69-70]	• QCM biosensor for selective determination. [71] • On-chip detection of protease biomarkers. [72] • Reflectance spectroscopy-based biosensors. [73] • pH-responsive biomedical materials. [74]
Poly(vinylpyrrolidone) (PVP) hydrogel.	Mechanical properties, elastic properties, and non-toxicity. [75]	• Wearable electronic biosensors. [76] • Ultra-Sensitive MicroRNA Biosensor. [77] • Hexavalent chromium sensing platform. [78] • Integrated microneedle biosensor. [79]

Table 3: Composite hydrogels used in biosensors

Name	Properties	Applications
Graphene Oxide (GO)	High surface area, hydrophilicity, and biocompatibility. [80]	• Fluorescent biosensor for antibiotic detection. [81] • Novel nitrite biosensor. [82] • Mechanically and thermally sensitive skin-like bioelectronics. [83] • Flexible glucose biosensor. [84]

Carbon Nanotube (CNT)	Pore structure, high conductivity, electrochemical stability, one-dimensional structure, low mass density, high mechanical strength, and high specific area. [85]	• Enhancing the detection sensitivity of electrochemical sensors. [86] • Making target-specific probes for biosensors. [87] • In an amperometric cholesterol biosensor. [88] • Bioanode for enhanced microbial electrocatalysis. [89]
Silica Nanoparticle	Physical, mechanical, thermal properties, and chemical stability. [90]	• In a glucose biosensor. [91] • Microarray biosensor for metal-enhanced fluorescence detection. [92] • In environmental monitoring. [93] • DNA-based biosensors and diagnostics. [94]
Gold Nanoparticle (AuNP)	Plasmonic effect, bio-functionalization, and large surface area. [95-96]	• Colorimetric detection of lead (II) and uranyl ions. [97] • LSPR-based biosensors. [98] • Acetylcholinesterase-based biosensor for carbamate detection. [99] • Dual DNA biosensor. [100]
Magnetic Nanoparticle (MNP)	Stimuli responsiveness, biodegradability, and biocompatibility. [101-102]	• AAmperometric biosensor design. [103] • Low-field nuclear magnetic sensing. [104] • Biosensor for ferrogel detection. [105] • Electrochemical biosensing. [106]
Quantum Dots (QD)	Bioconjugation, photoluminescence, and optical properties. [107-108]	• In multimodal biosensing. [109] • Fluorescence-based sensing platform. [110] • Electrochemiluminescence immunosensor. [111] • Enzyme-based optical biosensor. [112]
Conductive Polymer	Stimuli responsiveness, biocompatibility, and controllable electronic properties. [113-114]	• In doping engineering. [115] • Electrochemical biosensors. [116] • In biosensing functions of copious biological species. [117] • In noninvasive, real-time measurements. [118]

Table 4: Comparative summary of natural, synthetic, and composite hydrogels in biosensors.

Hydrogel type	Advantage	Limitations
Natural hydrogels (such as alginate, chitosan, gelatin, etc.) [9, 14, 18]	Good biocompatibility, biodegradable, similar to the cell and tissue environment.	Low mechanical strength, large batch variability, and limited stability.
Synthetic hydrogels (such as PEG, PAM, PVA, PNIPAM, etc.) [48-49]	Highly controllable performance, high mechanical strength, and functionalizable.	Poor biodegradability may present biocompatibility issues.
Composite/hybrid hydrogels (such as GO, CNT, AuNP, MNP, and other composite systems) [80, 85, 96]	Combining the advantages of natural and synthetic materials, diverse functionalities (conductivity, optical properties, etc.), and being suitable for intelligent and multimodal sensing.	Complex preparation, high cost, potential long-term stability, and safety concerns.

3. DESIGN AND FABRICATION OF HYDROGEL-BASED BIOSENSORS

Hydrogels can respond to specific compound, such as a biomarker or bioanalytes, in their surrounding medium or material. Depending on the biomolecule and bioanalyte incorporated into the hydrogels, these conjugate biomaterials can be easily tailored to respond to various biological conditions, which brings considerable potential for biosensor fabrication [116]. Advanced fabrication techniques are employed to precisely control a hydrogel's structure, properties, and functionality in the development of biosensors, enabling the creation of complex architectures and finely tuned materials with enhanced sensor performance. Here are these techniques applied in biosensors.

3.1 Photopolymerization

Photopolymerization is a stimuli-responsive technique that begins with the interaction of visible or UV light with light-sensitive compounds called photoinitiators, which generate free radicals that can initiate polymerization to form crosslinked hydrogels from either monomers or macromers **(Figure 1)** [119]. Three main classes of photoinitiation exist based on their mechanism: photocleavage reactions, hydrogen abstraction, and cationic reactions [120], providing a plethora of options for traditional polymerization methods to be explored in the field of photopolymerization, both in space and time. [121]

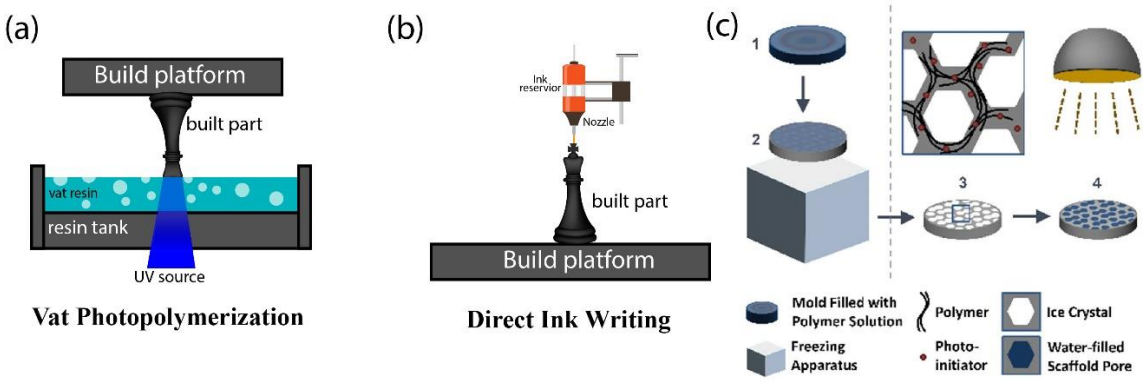

Figure 1. An illustration of the most popular hydrogel-based 3D printing methods: (a) vat photopolymerization (stereolithography (SLA/DLP) (Adapted from [122] under (CC BY) license), (b) direct ink writing (DIW) (Adapted from [122] under (CC BY) license), (c) photopolymerization of frozen polyethylene glycol (PEG) solutions with photoinitiators to form porous hydrogels, (Adapted with permission from [123]).

3.2 Electrospinning

Electrospinning is one of the highly resourceful techniques made in combination with electrospray and spinning, where electric field application to a droplet of a fluid acting as one of the electrodes leads to the melting down of droplet deformation and finally to the ejection of a charged jet from the tip of the cone moving forward to the counter electrode, leading to the formation of fine, continuous fibers in the end [124]. Hydrogels engineered with electrospinning techniques show excellent performance in biomedical applications and biosensors. The polymeric micro/nanofibers produced by these techniques can mimic the geometries of natural ECM by drawing micro/nanofibers from polymer precursors using electrical forces, followed by structural stabilization **(Figure 2)**. [125-126]

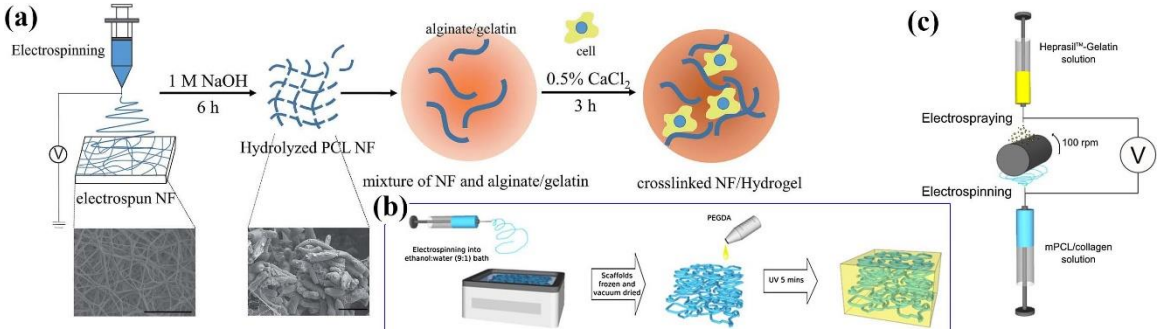

Figure 2. Schematic of the (a) presentation of preparing NF/hydrogel encapsulating cells by the electrospinning method, (adapted with permission from [127]) and (b) showing the assembly of electrospun poly(ε-caprolactone) nanofibers and poly(ethylene glycol)-diacrylate hydrogel to create a fully encapsulated and injectable composite scaffold (adapted with permission from [128]), and (c) representation comprising electrospun fibers coupled with hydrogels. (adapted with permission from [128]).

3.3 3D printing and microfabrication

3D printing, also known as additive manufacturing or rapid prototyping, is a versatile technology for fabricating 3D objects in successive layers by controlled addition of ink materials, following a predefined digital model designed with the help of Computer-Aided Design (CAD) [129]. Compared to conventional formative and substrate technologies, which typically require molds, tooling, and machining, 3D printing is more versatile because it enables the creation of more complex and elaborate substructures. 3D printing has been considered the next global industrial revolution, with tremendous contributions to the chemical, pharmaceutical, and biomedical fields [130]. A vital yet limiting part of the design and application of 3D printing is selecting suitable biomaterials for use as inks. 3D printing techniques for biomedical applications can be mainly classified based on their working principles: (i) laser-based systems by photopolymerization pathway, (ii) nozzle-based systems through the extrusion of (pre)polymers, and (iii) printer-based systems by material and binder jetting **(Figure 3)** [131-132]. Dutta et al. [133] discussed biodegradable 3D-printed hydrogel scaffolds of alginate, gelatin, and cellulose nanocrystals in bone tissue engineering. These scaffolds enhance cell adhesion, proliferation, and osteogenic differentiation, thereby improving bone regeneration. The main properties of these scaffolds (mechanical strength, biocompatibility, and mineralization efficiency) have been assessed herein, showing that they could have a place among biomaterials for tissue engineering applications.

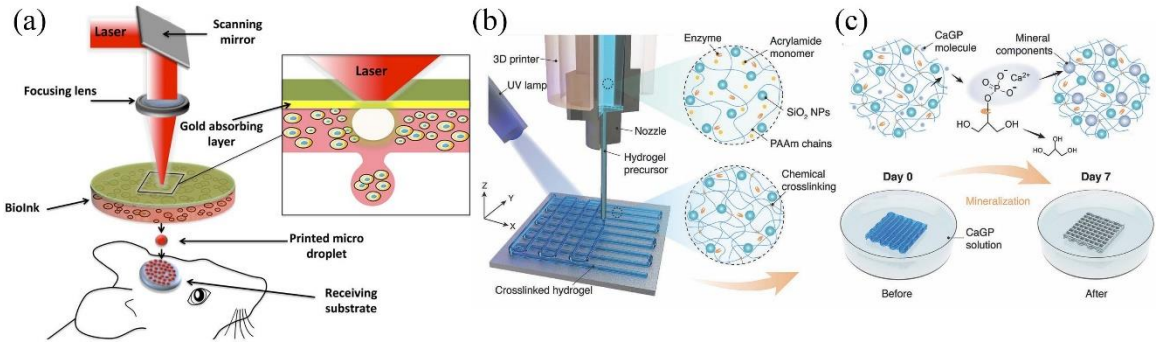

Figure 3. (a) Droplet deposition by laser-assisted 3D bioprinting process, (adapted with permission from [132]) (b) Using an extrusion-based 3D printer, alkaline phosphatase (ALP)-loaded hydrogel inks were produced into 3D structures. The physical interaction between silica nanoparticles and PAAm polymer chains results in a physically cross-linked hydrogel that immediately gels after printing and can be fluidized by shear force during ink extrusion. Induced covalent network creation with further UV curing results in the development of high-fidelity-shaped 3D hydrogel structures (adapted with permission from [134]), and (c) ALP enzyme catalyzes the dephosphorylation of calcium glycerophosphate (CaGP), which forms calcium phosphate ($Ca_3(PO_4)_2$) nanoparticles to harden the hydrogel substrates (adapted with permission from [134]).

Biosensors can be classified by signal transduction method, including optical, electrochemical, thermometric, piezoelectric, and magnetic methods, among others [135]. Hydrogels' distinct physicochemical responsiveness enables them to actively participate in signal generation across various biosensor modalities. Analysts alter the hydrogel's refractive index and light-scattering

properties, thereby altering the optical biosensor's response. This allows them to be detected with high sensitivity using plasmon resonance, absorption, or reflection. In electrochemical systems, hydrogels directly affect conductivity and current responses by controlling how redox species diffuse and how easily ions can pass through. Mechanical biosensors succeed because they can alter shape and size, thereby creating stress and strain that can be measured. Hydrogels are viscoelastic with high water content. This modifies how waves propagate and interact, enabling better acoustic sensing. Lastly, thermal biosensors transduce biochemical reactions into detectable temperature signals by exploiting variations in the heat capacity and phase transitions of hydrogels. These direct connections between transduction and hydrogel properties show that hydrogels can effectively serve as both structural scaffolds and biosensing enhancers. Bio-electrochemical biosensors extract information from living things to gauge their electrical properties. The bio-electrochemical sections form the core of data modification. Electrochemical biosensors interface the biochemical recognition agent with an electrode where current, potential, or impedance is measured as a result of the biochemical process [136]. Optical biosensors are essential for quantifying the quantity of a substance in a bioassay, the speed at which it binds, and also its molecular structure. Aimed at sorting and counting target analysts through transduction for quantitative bioassays, they have been employed for various optical phenomena, including reflection, absorption, fluorescence, and scattering-transmission and intensity [137]. The mechanical biosensor is an analytical method that may serve as a qualitative molecule finder. Mechanical biosensors convert biomolecular interactions into measurable mechanical responses, such as stress-induced deflections, shifts in resonance frequency, or cantilever bending. Recent developments include microfluidic-mechanical hybrids that enable real-time analysis of complex fluids without labeling, hydrogel-integrated mechanical biosensors that convert volume changes into measurable stress/strain signals, and nanocantilever-based devices that detect single-molecule binding events with very high sensitivity. These developments indicate that the field of biological mechanical sensing has matured into quantitative, sensitive, and, in some cases, clinically relevant detection beyond simple yes-or-no binary measurements [138]. Mechanically integrated biological sensing offers a new approach to measuring forces, displacements, and mass during cellular and subcellular processes. Mechanical biosensors are tiny cantilevers that can sense the biomolecule of interest. They may be either surface-stress or dynamic-mode sensors. [139]

Acoustic sensors are an essential tool across numerous scientific and technological domains, as they convert sound waves into electric signals [140]. Sensors, which are a category of transducers, typically measure a physical or chemical characteristic of an environment (e.g., temperature, pressure, biological/chemical concentration) and convert that measurement into an electrical, magnetic-optic, or acoustic signal. Biosensors turn biological data into numbers [141]. Acoustic wave devices can serve as sensors since they exhibit sensitivity to electrical, chemical, mechanical, or optical perturbations on their surfaces [142]. These sensors are used to detect minute traces of biomolecules by binding to biomarkers for pathogen and virus detection, as well as for early-stage cancer diagnosis [143]. Thermal biosensors are a type of biosensing technology that measures heat energy information released or absorbed during biochemical reactions using quantitative methods. Thermal biosensors enable quantitative monitoring of metabolic activity and enzymatic processes by converting the minute heat changes produced during biochemical reactions into quantifiable signals. Hydrogel-based microcalorimetric platforms for sensitive detection of microbial growth and nanomaterial-enhanced thermal transducers that significantly increase sensitivity and response time are recent advancements that bring this modality from theoretical demonstration to real-world biomedical applications [144]. This biosensing device detects temperature changes associated with biological processes and has proven applications in monitoring microbial growth. Additional fabrication techniques for hydrogel-based biosensors include physical cross-linking

and self-assembly via ionic or hydrogen bonding to create biocompatible, reversible matrices; chemical cross-linking (e.g., with glutaraldehyde or genipin) to form stable covalent networks; and freeze-thaw cycling, particularly for PVA hydrogels, to enhance mechanical strength. Sol–gel processing can be used to incorporate nanomaterials for optical and electrochemical sensing. For lab-on-a-chip applications, microfluidic-assisted fabrication enables accurate control of size and geometry in hydrogel droplets. These methods can synergize with photopolymerization, electrospinning, or 3D printing to complement the toolbox of strategies available for tuning hydrogel properties and biosensor activity. [145]

4. BIOMEDICAL APPLICATIONS

The intensive exploration of the chemical, mechanical, and biocompatible properties of stimuli-sensitive hydrogels has led to limitless applications in biological signal sensing across various medical/biological disciplines. Although accuracy is a significant problem, monitoring physiochemical changes using biosensors has facilitated the way towards early disease detection and its management [146]. Use of hydrogels in the development of innovative biosensors has expanded their utility to a variety of biomedical areas [147], as described below:

4.1 Clinical diagnostics

Biosensing devices made of hydrogel have become valuable, sensitive tools for clinical diagnosis in recent years, thanks to their high sensitivity, biocompatibility, and ease of modification with other molecules. Commercial glucose monitoring systems are limited by glucose's inability to diffuse deeply into the thick sensing layer, the lack of control over glucose oxidase leakage, and their susceptibility to mechanical damage. In the meantime, self-healing enzyme-functionalized hydrogel-integrated biosensors from chitosan and oxidized dextran may also be applied for glucose determination in an electrochemical or optical mode in an OSN assay, such as for glucose management in diabetes. The high sensitivity, biocompatibility, and flexibility of hydrogel biosensors have rendered them invaluable tools with great potential for clinical diagnostics. For example, mechanical instability, enzyme leakage, and glucose penetration into thick sensing coatings are problems for commercial glucose monitoring systems. As a promising new polymer material, hyaluronic acid hydrogels have shown enormous potential for biosensor applications due to their tunable sensitivity, low cost, and good biocompatibility, especially in fields such as continuous glucose monitoring and real-time health monitoring. These problems have been addressed by incorporating self-healing matrices and by improving the analysis of diffusion pathways with hydrogel-based designs. [148- 149]

Early cancer diagnosis is essential for effective disease prevention, but existing methods are not ideal. New biomaterials, including hydrogels, have promising potential for biosensor development in cancer detection [150]. Indeed, the development of anti-biofouling hydrogel-based biosensors for the early non-invasive detection of oral cancer in body fluids (such as saliva) is becoming increasingly popular [151]. Comprising functional hydrogels, these biosensors are combined with electrochemical or optical measurement techniques to detect biomarkers, including tumor necrosis factor-α (TNF-α), a key biomarker for oral cancer detection **(Figure 4)**. Hydrogel biosensors have also been demonstrated in recent research for early cancer detection. Tumor necrosis factor-α (TNF-α), an essential inflammatory biomarker for oral cancer, has been successfully expressed in saliva by electrochemical hydrogel-based biosensors with a limit of detection (LOD) of ~1 pg/mL, which is lower than the physiological scale needed for clinical screening. Furthermore,

hyaluronic acid hydrogel biosensors have been shown to enable the detection of hyaluronidase activity in serum samples with sensitivity as low as sub-ng/mL, demonstrating their utility for non-invasive cancer diagnosis. These examples show that hydrogel matrices are not only ideal microenvironments for the immobilization of biomolecules but also improve analytical accessibility by incorporating readily adjustable porosity, which, along with swelling, results in detection that is similar or even better than that of traditional biosensing platforms. However, a significant challenge in translating these advances from the laboratory to medical practice is biofouling (particularly in complex biofluids such as serum and saliva) that persists during technology deployment at the bedside. Transport of proteins to sensor surfaces, such as protein adsorption, non-specific binding, and enzymatic digestion, is often a limiting factor in sensor performance, leading to significant reductions in lifetime, sensitivity, and reproducibility. For example, the antifouling strategies reported include PEGylated hydrogels, zwitterion hydrogel coating, and nanocomposite hydrogel systems to mitigate these issues. These methods of non-specific interaction inhibition lack biological compatibility. Antifouling Strategies in Diagnostics and Therapeutics. It will be essential to continue advancing the integration of these antifouling strategies to bridge further the ``disconnect'' between clinical translation and optimal performance in tissue models. [152]

4.2 Drug delivery and monitoring

The system can modify drug release rates, dosages, site-specific delivery, and agents o deliver optimal therapeutic effects [153-154]. TDM (Therapeutic Drug Monitoring) has been used to assess whether drug concentrations are within an optimal therapeutic range [155]. Over the past few years, hydrogels have been marketed as one of the most promising and tunable materials in these domains. Hydrogel biosensors that sense glucose and release insulin via hysteresis, such as glucose oxidase-integrated hydrogels (GOx), can be employed. Release of the drug leads to an observable biochemical or physical change in hydrogel-based drug delivery systems via stimuli-responsive sensing. Glucose-responsive hydrogels that conjugate glucose oxidase (GOx) can detect high glucose levels via an oxidation reaction that produces hydrogen peroxide and gluconic acid. The resulting redox shift or local pH drop triggers hydrogel swelling and/or electrochemical signals that can be linked to insulin release [156-157]. Tumors sometimes exhibit an acidic microenvironment (TME), making pH-sensitive hydrogels particularly effective under certain conditions. These hydrogels can release drugs in a controlled manner when exposed to the acidic conditions of the tumor site, thereby reducing side effects in cancer treatment [158]. pH-sensitive hydrogels exploit the acidic tumor microenvironment by altering the hydrogel's charge density, swelling, and drug diffusion rate through the ionization of carboxyl or amine side groups. These changes can be observed optically or electrochemically. When bacteria secrete enzymes (such as proteases) or antigenic byproducts, hydrogel biosensors respond. Enzymatic cleavage of cross-links releases incorporated dyes or alters conductivity, which signals changes in the microenvironment caused by infection. Particular hydrogel-based biosensors respond to bacteria-induced micro-environmental changes (pH, enzymes, and antigens). In addition to direct or indirect bacterial surface receptors, hydrogel biosensors can also be used for the early diagnosis of bacterial infections in point-of-care monitoring. Additionally, by utilizing changes in fluorescence or color intensity, integrated reporter molecules, such as fluorophores or quantum dots, enable real-time visualization of drug release kinetics. These hydrogel systems allow for simultaneous therapeutic drug monitoring (TDM) and controlled drug release by converting biochemical stimuli into detectable physical or optical signals. [159]

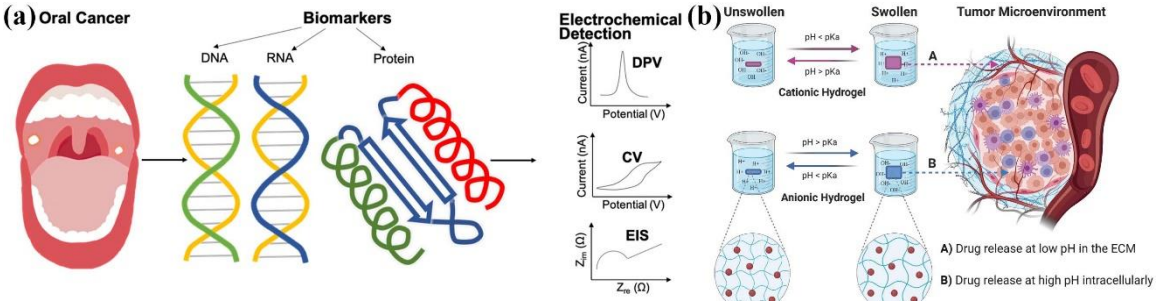

Figure 4. Schematic diagram of the (a) process of detecting oral cancer using an electrochemical biosensor (Adapted from [152] under (CC BY) license) and (b) pH-sensitive hydrogel swelling. Hydrogel swelling occurs through the ionization of side chain groups, which increases the hydrophilicity of the polymer chains and enhances the electrostatic repulsion between them. ECM, extracellular matrix, hydrogen ion H^+, hydroxyl ion OH^-. Red circles represent drugs loaded in the hydrogels. (Adapted from [160] under (CC BY) license).

4.3 Tissue engineering and regenerative medicine

Hydrogels are now being used as artificial extracellular matrices to more closely recapitulate the (patho)physiological features of human tissues [161]. 3D bio-printed hydrogel-based tissue models are emerging as an approach due to their ability to mimic native ECM (Extracellular Matrices) and to encapsulate cells. Hydrogel-based biosensors can monitor cellular and microenvironmental processes in real time; they have become essential tools in tissue engineering and regenerative medicine. The addition of bio-sensing capabilities to hydrogel scaffolds enables dynamic feedback that can direct tissue regeneration and simulate the extracellular matrix (ECM) [162-163]. Hydrogels can more closely recapitulate the mechanical and biochemical key features of human tissues due to their high water content, softness, reticulated structure, and, most importantly, their molecular diffusing ability, which is similar to that of human tissues [164-165]. For this reason, hydrogel-based biosensing tools are now being used to regenerate bone, cartilage, skin, and neural tissues widely **(Figure 5)** [166]. Additionally, 3D-printed electrically conductive hydrogels are utilized in cardiac tissue engineering, which seeks to repair cardiovascular damage. The low immunogenicity of the hydrogels in vivo may be beneficial for cardiac tissue engineering **(Figure 6)**. Hydrogels with integrated biosensors enable continuous monitoring of pH, oxygen concentrations, and enzymatic activity at the wound site during skin and wound healing. To hasten healing, this real-time feedback can help optimize therapeutic interventions, such as electrical stimulation or controlled drug release. Moreover, intelligent hydrogel biosensors for organ-on-a-chip systems are being developed to mimic physiological conditions and track tissue responses, with practical applications in transplantation and drug screening. [167-169].

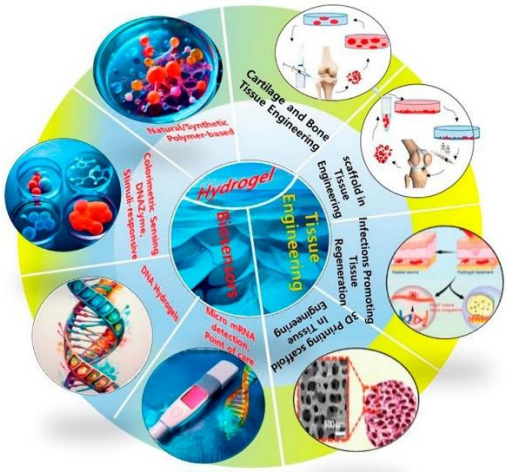

Figure 5. Schematic showing different hydrogel biosensor designs and tissue engineering applications, and their respective functions. (Adapted from [166] under (CC BY) license)

Hydrogel-based biosensors hold great potential for applications in neurodegenerative disorders (Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS)). Alkaline phosphatase (ALP) activity and calcium ion deposition can be detected by hydrogel-biosensor composites, which have been helpful for bone tissue engineering. TNF-α, and other inflammatory cytokines are essential markers of tissue integration and repair. Biosensor-embedded hydrogels have been used to detect them in cartilage regeneration. Cellulose and its derivatives-based biosensors show great promise for applications in sensing technology due to their renewability, biocompatibility, and chemical tunability. Similarly, conductive hydrogel-based biosensors in neural tissue engineering can monitor neurotransmitter activity and record electrical impulses, aiding the evaluation of neural network reconstruction and functional recovery [170-172]. These bio-sensing tools based on hydrogel also have regenerative medicinal implications due to their uniquely tailored properties, such as wound healing [173] and skin regeneration (skin grafting) [174], as well as organ regeneration and transplantation. [175]

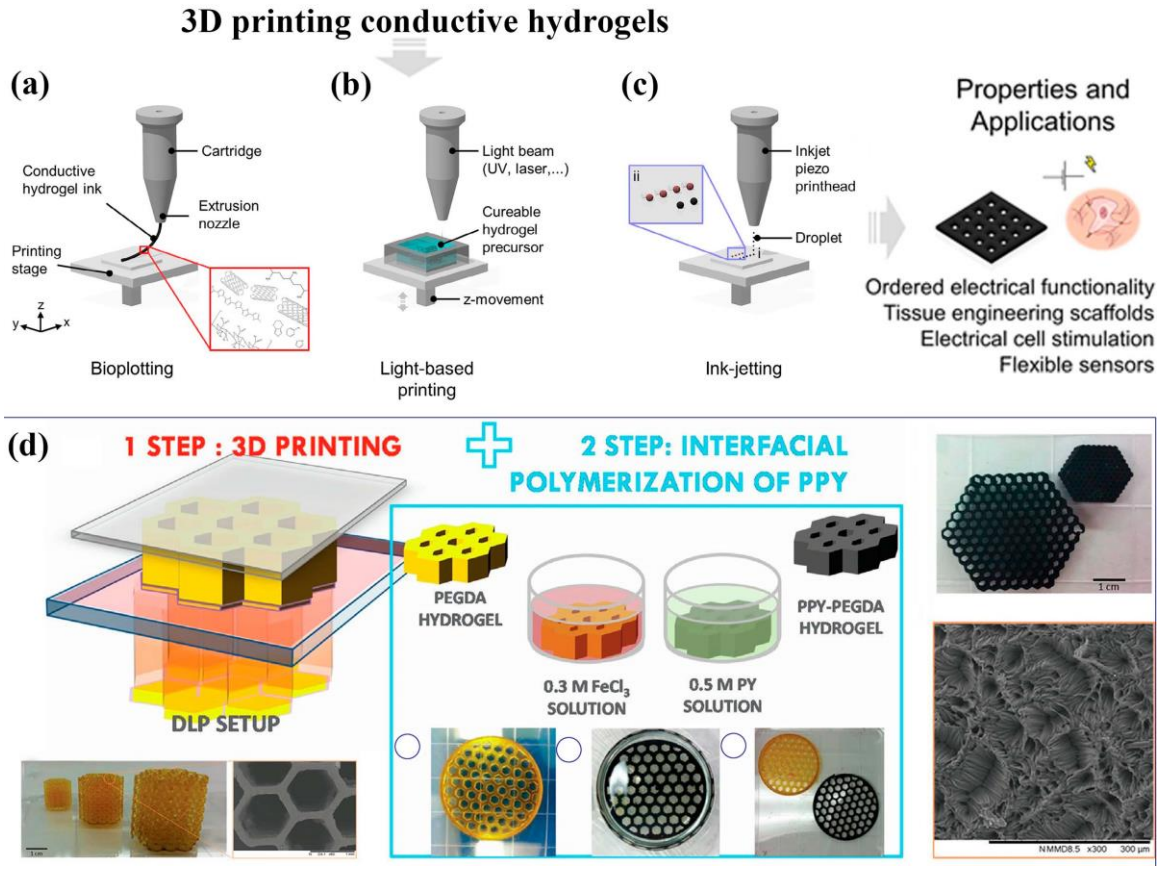

Figure 6. 3D printing technologies for processing conductive hydrogels. (a) Bioprinting (b) Light-based photo printing (c) Simultaneous deposition inkjet printing, (Adapted with permission from [167]) (d) Methyl orange (MO), the dopant of polypyrrole (PPy), and phenyl bis (2,4,6-trimethyl benzoyl)phosphine oxide, the photo initiator (PI), were used to print the PEGDA scaffold by DLP. The construct was printed, then submerged in a solution of $FeCl_3$ to start the oxidative polymerization of pyrrole (Py). This created in situ polypyrrole within the hydrogel matrix, increasing its electrical conductivity (Adapted with permission from [168]).

4.4 Wearable and implantable devices

Applications of micro biosensing devices in connecting technology and personalized medicines are soaring, and incorporating hydrogels into these devices has brought a novel approach to this field [176]. Despite the challenges of being an all-in-one sensor, hydrogel-fused devices that integrate long-term biological functions, multimodal responsiveness, and therapeutic capabilities have attracted growing interest as wearable and implantable devices [177]. Although wearable and implantable hydrogel-based devices have considerable potential, several significant obstacles stand in the way of their clinical translation. Because hydrogels are susceptible to degradation, structural fatigue, and biofouling from protein adsorption or fibrotic encapsulation, all of which impair signal accuracy, long-term in vivo stability remains a challenge. As miniaturized systems must guarantee safe, continuous operation without heat generation or signal loss through tissue, where attenuation and scattering can reduce fidelity, dependable wireless power and data

transmission are additional constraints. Since chronic implantation frequently causes inflammation, immunological reactions, or mechanical mismatches with host tissue, maintaining proper biocompatibility is challenging after short-term tolerance. Innovations such as mechanically reinforced composites, immune-responsive materials, antifouling hydrogel coatings, and low-power wireless communication techniques are necessary to overcome these obstacles and ensure reliable, long-lasting, and clinically feasible device performance. Various wearable devices have been designed to implement hydrogel-integrated biosensors, including hydrogel smart patches [178], electronic tattoos (e-Tattoos) [179], hydrogel foot insoles [180], and hydrogel neckbands [181]. Moreover, implementable devices are also developed along with wearable to support the human body with real-time monitoring, wireless connectivity, and minimally invasive designs, likely hydrogel-based glucose monitors for continuous glucose monitoring [182], drug delivery implants [183], neural implants [184], hydrogel ocular implants [185], and wound healing implants. [186]

5. CONCLUSION AND OUTLOOK

This paper systematically summarizes the different types of hydrogel properties and biosensor applications, including the design and fabrication of hydrogels. In the future, researchers envision that hydrogels will function intelligently and autonomously according to environmental changes. Over the last century, the understanding and engineering of the human body have advanced through interdisciplinary efforts in modern medicine, biology, and biomedical engineering. In particular, the double-crosslinked polymer hydrogel composite exhibits excellent mechanical and self-healing properties. It has enormous potential in the biomedical field, especially in tissue engineering and wound dressings. At the same time, polymer hydrogel complexes also have significant application value for the delivery of hydrophobic drugs or for co-delivery. As hydrogels continue to develop, their biosensor applications will become increasingly widespread while continually adapting to biomedical needs. Future research on hydrogel-based biosensors is expected to provide more inspiration and support for the development and innovation of related fields.

The most promising candidates for near-term commercialization in biosensing are synthetic and composite hydrogels, particularly PEG-based systems, due to their tunable chemistry, and hybrid nanocomposite hydrogels (e.g., graphene oxide, gold nanoparticles, or conductive polymers) for their multi-functionality. This is because they combine stability, scalability, and biocompatibility. Key challenges include scalable, reproducible manufacturing of clinical--grade devices, assurance of long--term in vivo stability and antifouling performance, and enabling reliable multi-analytic detection under intricate physiological conditions. The development of intelligent self-healing and stimuli-responsive materials, the implementation of modern computational approaches, such as machine learning, for predictive hydrogel design, and the hybridization with flexible and wireless bioelectronics for real-time monitoring are thus likely to be key factors in future improvements. Interdisciplinary strategies to address these restrictions may advance hydrogel-based biosensors from the laboratory-prototype stage toward practical clinical hemostatic control, personalized drugs, and diagnostics. Hydrogel-based biosensors are highly attractive due to their biocompatibility, flexibility, and tunability. However, many problems with such an approach remain unsolved, including long-term stability, fabrication variation, and electronics integration. In the future, reasonably efficient regeneration must be achieved with smart hydrogel and composite scaffolds through advanced preparation technologies (e.g., three-dimensional printing) with large-scale production capacity and reproducibility support (facilitated by multidisciplinary cooperation), to boost rediscovery for clinical research validation. These strategies endow the

hydrogel biosensors with reliable and sensitive platforms for future biomedical treatments, therapies, and agendas.

List of abbreviations

- AD : Alzheimer's Disease
- ALP : Alkaline Phosphatase
- ALS : Amyotrophic Lateral Sclerosis
- AuNP : Gold Nanoparticle
- CAD : Computer-Aided Design
- CaGP : Calcium Glycerophosphate
- CNT : Carbon Nanotube
- DLP : Digital Light Processing
- DIW : Direct Ink Writing
- ECL : Electrochemiluminescence
- ECM : Extracellular Matrix
- GelMA : Gelatin Methacrylate
- GO : Graphene Oxide
- GOx : Glucose Oxidase
- HSA : Human Serum Albumin
- LSPR : Localized Surface Plasmon Resonance
- MNP : Magnetic Nanoparticle
- NF : Nanofiber
- PAAm : Polyacrylamide
- PD : Parkinson's Disease
- PEG : Polyethylene Glycol
- PHEMA/pHEMA : Poly(2-hydroxyethyl methacrylate)
- PNIPAM : Poly(N-isopropylacrylamide)
- PMAA : Poly(methacrylic acid)
- PVP : Polyvinylpyrrolidone
- QD : Quantum Dot
- QCM : Quartz Crystal Microbalance
- SLA : Stereolithography
- TDM : Therapeutic Drug Monitoring
- TME : Tumor Microenvironment
- TNF-α : Tumor Necrosis Factor-alpha

Author Contributions

Hrittick Saha, Bonhi Dey, and Khan Rajib Hossain: Conceptualization, methodology, and resources. Software, Hrittick Saha, and Bonhi Dey implemented, validated, and formally analyzed the model. Hrittick Saha and Bonhi Dey also performed investigation, data curation, and visualization. Hrittick Saha and Bonhi Dey wrote the original draft of the manuscript; Khan Rajib

Hossain performed writing review and editing, supervision, and project administration. All authors have read and agreed to the manuscript as written.

Conflicts of Interest The authors declare that they have no known financial or interpersonal conflicts that would have appeared to impact the research presented in this study.

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