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Hierarchical Engineering for Biopolymer-based Hydrogels with Tailored Property and Functionality

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Biopolymer-based hydrogels offer versatility in biomedical engineering due to their abundance, biocompatibility, tailorable properties, and environmental responsiveness. Realizing their full potential requires understanding the molecular-level design principles that govern their macroscopic behavior. This review analyzes recent advances in the molecular engineering of biopolymer-based hydrogels, emphasizing innovative network design strategies and processing methods for precise control over material properties and functions. How molecular design influences hydrogel behavior across multiple length scales are explored, focusing on: 1) network design strategies: approaches like double networks, interpenetrating networks, and supramolecular assemblies to tailor mechanical and responsive properties; 2) processing techniques: methods such as Hofmeister effect-induced chain aggregating, cononsolvency-based porous structure controlling, and directional freezing-induced network alignment to achieve hierarchical and anisotropic structures. How these design principles and processing methods influence critical hydrogel properties like mechanical strength, inner mass transportation, and degradation are discussed. The review also covers advanced fabrication techniques that leverage these molecular engineering approaches to create complex, functional hydrogels. By elucidating the relationships between molecular architecture, processing methods, and resulting material properties, this work aims to provide a framework for designing next-generation biopolymer-based hydrogels with enhanced performance and functionality across various applications.

1. Introduction

All lifeforms exist in gel states, with biofluid serving as the liquid phase dispersed in the biomacromolecules-formed solid phase.[1] Biopolymer-based hydrogels, as their closest replicates, have emerged as a promising class of biomaterials, offering unique advantages over their synthetic counterparts. Composed of naturally occurring macromolecules such as polypeptides (e.g., collagen, gelatin) and polysaccharides (e.g., alginate, chitosan), biopolymer-based hydrogels closely inherited their biophysical and biochemical nature.[2] This bio-derived nature confers biopolymer-based hydrogels enhanced biocompatibility,[3] biodegradability,[4] viscoelasticity[5] and responsiveness.[6] Outstanding biocompatibility and biodegradability[7] make them ideal candidates for both in vivo and in vitro biological applications, including sutures, implants, scaffolds, wound dressing, and artificial organ replacements.[8] Their existence addresses concerns about the inflammatory response of tissues to cytotoxic synthetic materials and the long-term accumulation of synthetic material micro-debris in the body.[9] Furthermore, the viscoelasticity and responsiveness of biopolymers allow for precise and wide-range customization over the mechanical properties,[10] stability/dynamicity,[11] and functionalities of biopolymer-based hydrogels, which enables tailoring the biopolymer-based hydrogel properties for specific applications, not only in biomedical fields such as tissue engineering[12] and drug delivery[13] but also in several cutting-edge applications such as soft robotics[14] and bioelectronics[15] (**Figure 1**). In addition to their biomedical advantages, biopolymer-based hydrogels offer a more sustainable and eco-friendly alternative to conventional synthetic hydrogels. Derived from renewable resources and often produced through energy-efficient, environmentally benign processes, biopolymers help reduce reliance on petrochemical feedstocks and mitigate the ecological burden associated with persistent synthetic polymers. Such attributes align with global efforts to develop green and sustainable materials, ultimately enhancing the appeal and potential of biopolymer-based hydrogels in diverse application areas.

The central challenge in biopolymer-based hydrogel engineering lies in precisely controlling material properties and functionalities by hierarchically tailoring material structures across whole-length scales.[16] At the molecular scale, polymer composition, chain interactions, cross–linking strategies, and chain configurations establish the foundation of the hydrogel network.[17]

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DOI: 10.1002/adma.202414897

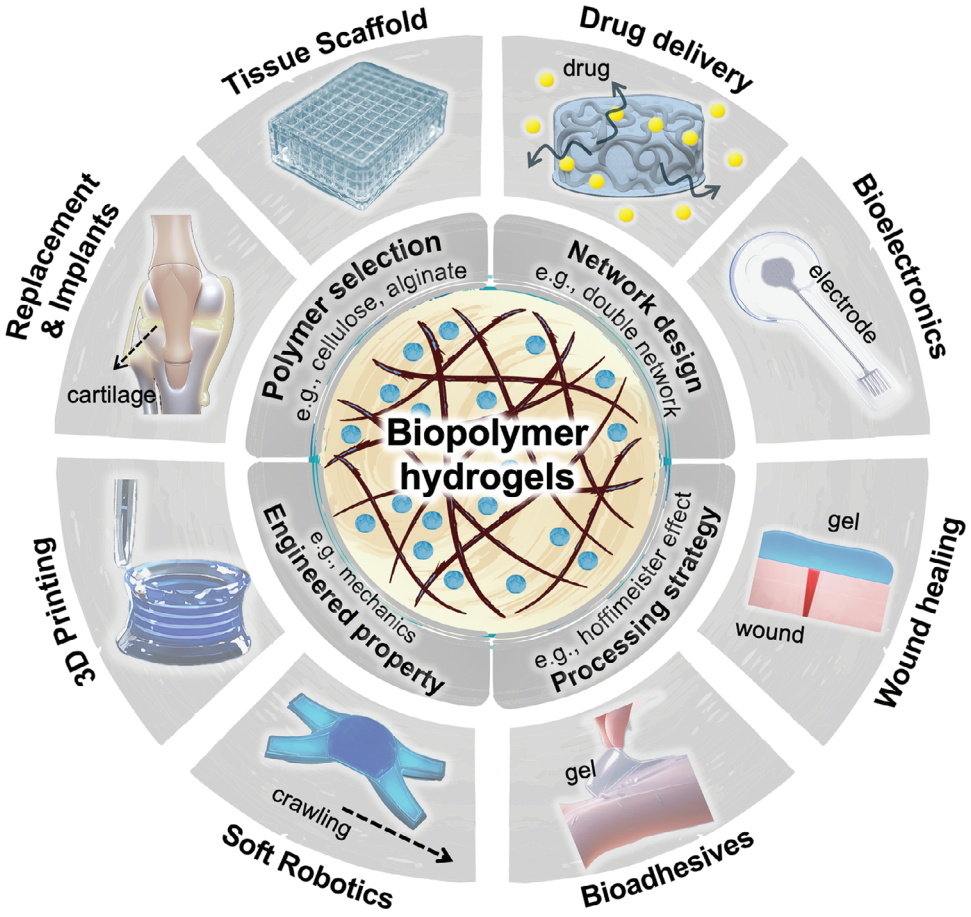

Figure 1. Schematic illustration of the biopolymer-based hydrogel design-to-application pipeline. The key stages in development are depicted, with polymer selection, network design, and processing strategies. The hydrogel's properties and applications are influenced by the relationships between these stages, enabling usage across biomedical, environmental, and engineering fields.

These molecular arrangements then influence their mesoscale structures, which further dictate macroscopic properties such as mechanical strength, diffusion characteristics, and stimuli responsiveness.[18] The dynamic nature of biopolymeric materials is both an opportunity but also a challenge, as continuous molecular rearrangements and reversible bond exchanges allow dynamic tuning of the material properties in both pre-fabrication and post-fabrication stages across all scales while threatening their robustness and long-term stability.[19]

Guided by the experience of 3.8 billion revolutions, nature has proved the possibility to build all kinds of tissues, either stiff (e.g., tendon)[20] or soft (e.g., liver),[21] stable (e.g., cartilage)[22] or dynamic (e.g., muscle), by carefully manipulating and arranging the biopolymers. Such comprehensive understanding spanning from molecular design principles to processing strategies and ultimately to the desired functionality in specific biomedical applications is essential but still lacking for artificial biopolymer-based hydrogels. By elucidating such molecular feature-microscopic structure-macroscopic property relationships, we aim to enable the rational design of biopolymer-based hydrogels with tailored properties for targeted applications. This approach will facilitate the development of advanced materials that can meet the complex demands of in vivo environments, such as controlled degradation, mechanical matching with host tissues, and spatiotemporal presentation of bioactive cues, as well as promoting the generation of robust functional biomass-based materials for bioelectronics and soft robotics.[23]

This review examines biopolymer-based hydrogel engineering approaches that bridge molecular features, multi-scale structures, and macroscopic functions. By analyzing how molecular structure, interactions, and assembly processes of biopolymers influence hydrogel properties across different length scales, we seek to provide insights into the rational design of these materials. Our discussion centers on several key aspects, such as network design, processing strategies, and dynamic behavior, by summarizing how these factors individually and collectively impact hydrogel performance. We explore molecular and network design strategies for tailoring microscopic structures and properties. Additionally, we examine advanced network design strategies and processing methods and their influence on hydrogel structure and function, highlighting how processing methods affect the final material characteristics. Then we listed the current theoretical model for describing the mechanical performance, mass transportation, and degradation profile of biopolymer-based hydrogels, providing insight into the structure-property relationship. Advanced fabrication techniques were also

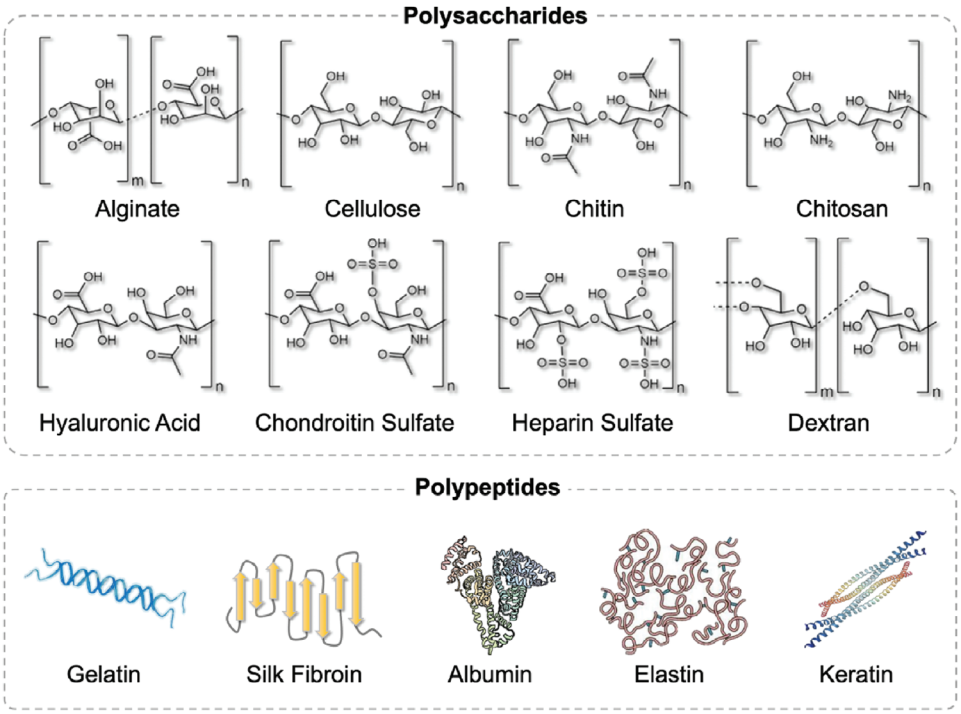

Figure 2. Molecular structures of common biopolymers used in hydrogel design. Top: Chemical structures of key polysaccharides including alginate, cellulose, chitin, chitosan, hyaluronic acid, chondroitin sulfate, heparin sulfate, and dextran. Bottom: Schematic representations of polypeptide structures for gelatin, silk fibroin, albumin, elastin, and keratin.

then encapsulated, which is inevitable for precisely shaping and tuning the biopolymer-based hydrogels. By summarizing and coupling the relationships between network design, processing, and hydrogel properties, we aim to provide a comprehensive overview that connects molecular design, microscopic structures, and macroscopic performances. Furthermore, we discuss emerging applications that leverage controlled hydrogel properties, illustrating how molecular-level engineering contributes to the development of advanced materials for specific uses. Our objective is to present researchers with systematic approaches for developing hydrogels with tailored characteristics, thereby contributing to the ongoing advancement of materials with enhanced control over structure, properties, and function in fields such as biomedical engineering and active materials with yet-to-imaginable performances.

2. Overview of Biopolymers

Biopolymers serve as fundamental building blocks for biopolymer-based hydrogel networks, offering distinct advantages in biocompatibility, biodegradability, and structural versatility. This review focuses primarily on two major classes of biopolymers: polysaccharides and polypeptides, which form the backbone of many advanced hydrogel systems.

2.1. Polysaccharides

Polysaccharides represent a diverse class of biopolymers abundantly sourced from plants, microorganisms, and animal tissues (**Figure 2**). Cellulose, the most prevalent biopolymer on Earth, is derived from plant cell walls and consists of D-glucose units linked by β-1,4 glycosidic bonds.[24] Its strong microfibril crystal structures impart impressive mechanical properties, both as a standalone material and as reinforcement in hydrogel matrices.[25] Chitin, primarily sourced from crustacean shells, shares a similar structure to cellulose but with acetamide groups replacing hydroxyls, resulting in *N*-acetyl-D-glucosamine repeat units.[26] This substitution enhances hydrogen bonding, leading to increased strength in the chitin fibrillar matrix compared to cellulose. Chitosan, produced by deacetylating chitin, consists of glucosamine and *N*-acetyl-D-glucosamine units.[27] Its degradation rate and hydrophilicity can be tuned by adjusting the degree of deacetylation, which typically ranges from 30% to 95%.

Alginate, another linear polysaccharide, is composed of β–D-mannuronic acid (M) and α-L-guluronic acid (G) residues. Originally found in brown algae cell walls, it provides a flexible mechanical structure that protects seaweed from strong water currents.[28] Alginate's ability to rapidly cross–link with divalent cations (e.g., Ca^{2+}) through ionic interactions with G residues, combined with its low cost and toxicity, makes it a favored material for biomedical hydrogels.[29] Hyaluronic acid (HA), a linear glycosaminoglycan (GAG) consisting of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine units, is a native component of the extracellular matrix (ECM).[30] Found in various tissues including cartilage, muscle, and skin, HA's high hydrophilicity results in highly water-swollen hydrogels that mimic the properties of many tissues and organs.[31] This characteristic makes HA-based hydrogels ideal for applications such as wound dressing, intra-articular injections, and soft-tissue dermal fillers.

Chondroitin sulfate, another important GAG, consists of 40–100 repeat units of alternating β-1,3-linked-N-acetylgalactosamine and β-1,4-linked-glucuronic acid.[32] As a major component of aggrecan, it plays a crucial role in cartilage mechanics by influencing tissue hydration, swelling, and lubrication.[33] Heparin, a linear GAG composed of uronic acid and D-glucosamine units, is found on cell surfaces and in the ECM.[34] It plays essential roles in tissue development, angiogenesis, and anticoagulation, and is one of the few clinically approved polysaccharide drugs.[35] Dextran, a highly branched polysaccharide of α-1,6-linked glucose monomers with α-1,3 branches, is a major component of bacterial extracellular matrices.[36] It facilitates surface adhesion and biofilm formation and has been extensively researched in dental applications, particularly in the context of streptococci-secreted dextran forming gelatinous plaques on teeth.

2.2. Polypeptides

Polypeptides are biopolymers consisting of amino acid repeat units, classified as proteins when they exceed 50 amino acids in length (Figure 2).[37] Polypeptide- and protein-based biopolymer-based hydrogels, including gelatin, albumin, silk fibroin, and elastin, have garnered significant interest in biomedical applications due to their capacity to incorporate numerous cell interaction sites and mimic native extracellular matrix functions.[38] These polypeptides can be isolated from human, animal, or plant sources, or engineered synthetically using recombinant protein production or peptide synthesizers. The precision and diversity offered by polypeptide materials make them particularly attractive for various biomedical applications.[39]

Gelatin, a hydrolyzed and denatured form of collagen, exemplifies the versatility of protein-based biopolymer-based hydrogels.[40] Derived from collagen, the primary structural protein in mammalian connective tissue ECM comprising 25–35% of total protein content, gelatin is typically extracted from animal skin and bones through acid or alkaline treatments followed by thermal separation. The resulting gelatin structure retains some cell-binding sequences from collagen, including RGD (Arg-Gly-Asp) motifs that enable integrin-mediated cell adhesion.[40a] While gelatin preserves portions of the Gly-X-Y amino acid repeats from collagen, the denaturation process disrupts the native triple helix-forming capability. Instead, gelatin chains can form partial helical structures and physical cross–links through temperature-dependent chain associations, which contribute to its thermo-responsive gelation behavior. Incorporating gelatin into biomaterials has been shown to enhance cell integration and tissue repair in numerous applications. Silk, another prominent protein-based material, is produced by various arthropods including silkworms, spiders, scorpions, and bees. It consists of two major proteins: silk fibroin, a semicrystalline protein providing structural stiffness and strength, and sericin, a glue-like protein that encases silk fibroin to bind fibers together.[41] Silk fibroin's excellent mechanical strength, biodegradability, and widespread availability make it particularly valuable for biomedical applications.[42]

Albumin, an endogenous protein produced primarily by the liver and secreted into blood plasma, has long been used clinically as a plasma expander to restore and maintain circulating blood volume following trauma, surgery, and blood loss.[43] While human serum albumin (HSA) remains the standard, bovine serum albumin (BSA) is increasingly explored as a more cost-effective and abundant alternative.[44] Elastin, a major component of elastic fibers crucial for resilience and elasticity in vertebrate connective tissues, is composed of tropoelastin precursors that accumulate on the microfibrillar skeleton.[45] With a half-life of ≈70 years in humans, elastin is an extremely durable biopolymer with low turnover in healthy tissue.[46] Elastin-based materials are of particular interest in fabricating hydrogel scaffolds for tissue engineering applications due to their diverse biological and mechanical properties stemming from elastin polypeptides' unique resilient behavior. Keratin, a cysteine-rich fibrous protein found in various animal integuments such as skin, hair, nails, wool, feathers, scales, and horns, serves structural and protective functions.[47] Its growing interest as a sustainable and economical raw material in the biomedical field is attributed to its easy sourcing from the millions of tons of wool and feathers produced annually as livestock industry byproducts.[48] Despite the diverse applications of polypeptide-based hydrogels, scaling up their production for industrial use can be challenging. Obtaining high-quality protein sources at large volumes often depends on animal tissues or specialized recombinant techniques, which can increase costs and introduce batch-to-batch variability. Ensuring consistent protein purity, maintaining stable tertiary structures, and controlling cross–linking density at scale requires careful optimization of extraction, purification, and processing protocols.A direct comparison of the key properties of polysaccharides and polypeptides is presented in **Table 1**.

3. Tailoring Biopolymer-based hydrogels' Properties

Hierarchical engineering is the foundation for creating biopolymer-based hydrogels with desired functionalities and elevated performances.[49] Diverse toolkits have been developed in both network design and processing techniques and have been proposed for tailoring material properties through strategic design. At the core of these approaches are a few key merits, each with distinct advantages and limitations.

3.1. Network Design Strategies

3.1.1. Molecular-level Interactions

Macroscopic performances of biopolymer-based hydrogels are significantly dictated by how the chains associate with the network and what network configuration they are formed.[16a] As introduced above, polysaccharides have multiple hydroxyl groups (—OH) on their repeat units, which contribute significantly to their hydrophilicity and hydrogen bonding capabilities.[50] Proteins, on the other hand, form hydrogen bonds primarily through their peptide backbone (—NH—CO—). While some amino acid side chains contain hydroxyl groups (serine, threonine, tyrosine), the majority of protein hydrogen bonding comes from the peptide bonds themselves. Amino groups —NH_2) are found at the

Table 1. Key Properties of Polysaccharides and Polypeptides.

Category	Polysaccharides	Polypeptides
Network Architecture	Random Coil	α-helix, β-sheet
Macroscopic Properties	Viscoelastic; Low Strength; High Water Retention	Elasticity; Strength Tunability; Strain-Hardening
Biofunctional Interface	ECM Mimicry; Protein Interaction; Glycoproteins	Ligand Design; Bioactive Sequences
Environmental Response	pH/Ion Sensitive	Thermoresponsive Folding
Processability	Solvent Casting; Extrusion	Self-Assembly
Degradation Mechanism	Enzymatic Hydrolysis; Biodegradable	Protease Degradation; Sequence-Dependent Stability
Cost & Scalability	Abundant; Low Cost	High Cost; Biotech-based Scalability

N-terminus of proteins and in certain amino acid side chains (lysine, arginine), while polysaccharides like chitosan contain amino groups in their repeat units.[51] These functional groups are capable of cross–linking the biopolymer chains in an aqueous environment by weak but abundant physical interactions. For example, alginate can effectively gelate by getting mixed with multivalent metal ions, which could cross–link the chains by ion-ligand coordination into a three-dimensional network[52] (**Figure 3a**). Similarly, but stronger is that biopolymers with highly regular or sequenced functional group arrangement, such as hydroxyl groups in cellulose and amino pairs in polypeptides, could form more stable interchain bonding by nanometer-scale assemble structures like nanocrystalline and triple helix[53] (Figure 3b,c). Other than these, abundant functional groups on biopolymer chains also encourage chemical modification of the polymer chains and introduce chemical cross–linking, dynamic covalent bonds, and other physical interactions into biopolymer-based hydrogel, forming biopolymer-based hydrogel with elevated performances. Chemical modifications of biopolymers provide powerful ways to introduce desired functionalities and control network properties[50] (Figure 3d). Common strategies include: methacrylation of hydroxyl/amine groups to enable photo-cross–linking [e.g., gelatin methacrylate (GelMA), hyaluronic acid methacrylate (HAMA)]; oxidation of hydroxyl groups to aldehydes for dynamic imine bonding (e.g., oxidized alginate); and conjugation of guest molecules (like adamantane or β-cyclodextrin) for host-guest interactions. Degree of modification can be tuned to control cross–linking density, mechanical properties, and degradation rates. Additionally, chemical grafting of synthetic polymers onto biopolymer backbones can combine the advantages of both natural and synthetic materials.

3.1.2. Network Architectures

Other than numerous design options at the molecular level, network characteristics also decide their overall properties. Most biopolymer-based hydrogels possess inherent dynamic networks through various reversible supramolecular interactions specific to their molecular structures. For polysaccharides, these include reversible calcium-carboxyl coordination in alginate, β-sheet aggregation in cellulose, and pH-dependent electrostatic interactions in chitosan. For proteins and polypeptides, these include hydrophobic associations, multiple hydrogen bonds between peptide sequences, and metal-coordination with specific amino acid residues. These naturally occurring reversible interactions, together with water-mediated hydrogen bonding networks, create dynamic networks that can temporarily

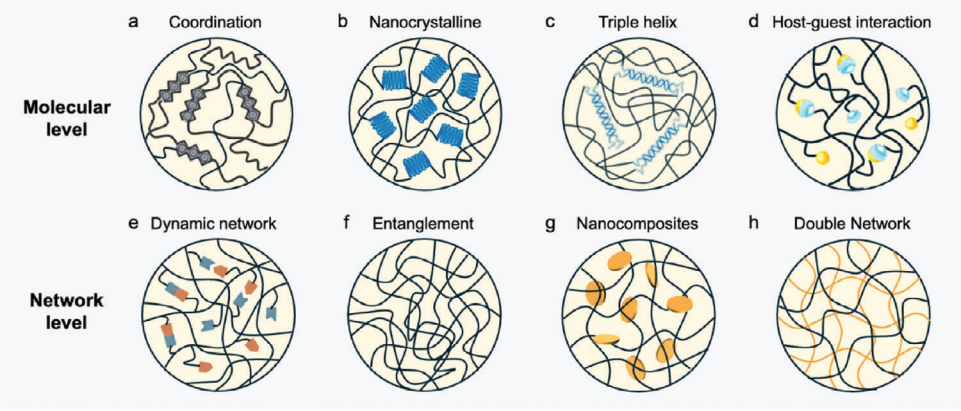

Figure 3. Schematic representation of network design strategies for biopolymer-based hydrogels at molecular and network levels. a–d) Molecular level: a) Coordination: Cross–linking through metal ion coordination bonds. b) Nanocrystalline: Formation of ordered nanocrystalline regions within the network. c) Triple helix: Formation of triple helix structures in some biopolymers like collagen. d) Host-guest interaction: Introduction of engineered molecular interactions. e,f) Network level: e) Dynamic network: Incorporation of reversible bonds enabling adaptability. f) Entanglement: Physical cross–linking through polymer chain entanglement. g) Nanocomposites: Incorporation of nanoparticles for reinforcement and added functionality. h) Double Network: Interpenetrating networks of two distinct polymer types.

disassemble and reassemble, leading to their characteristic viscoelasticity and stimuli-responsiveness (Figure 3e). As biopolymers typically have high molecular weights (>10 kDa), they can exhibit chain entanglements that contribute to network properties, though the degree of entanglement is more moderate compared to synthetic polymer networks formed through in situ polymerization. These entanglements can work alongside other interactions like hydrogen bonding and ionic cross–linking to influence mechanical properties. The extent of entanglement depends on processing conditions, polymer concentration, and solvent quality, requiring careful control during hydrogel preparation to achieve desired network structures[54] (Figure 3f). Such network structures have been proven to be promising for settling several traditionally contradictory material properties and achieving better overall performance.[55]

Nanomaterial composition is another powerful means to enhance mechanical properties and introduce novel functionalities in biopolymer-based hydrogels[56] (Figure 3g). Most of the nanoparticles are charged, thus, they could strengthen the network by serving as cross–linking sites through electrostatic interactions. Besides, taking advantage of their anisotropic feature, functionalized biopolymer-based hydrogels with anisotropic structures could be easily delivered. In addition, biopolymers are classic secondary components for fabricating double network hydrogels with outstanding performances[57] (Figure 3h). Biopolymer-based hydrogels that can withstand high stress while maintaining flexibility could be realized by using a brittle biopolymer as the first network combined with a ductile synthetic polymer network (like PAAm) as the second interpenetrating network.[58] However, the complexity of these systems can present challenges in preparation and may lead to irreversible network damage under extreme deformation.

3.1.3. Synergistic Design Approaches

The strategic combination of these approaches enables precise control over multiple key properties of biopolymer-based hydrogels. From a mechanical perspective, the modulus can be tuned from kilopascals to megapascals, while strain at break can be adjusted from 100% to over 2000%. The stress relaxation behavior and toughness (up to several MJ m^{-3}) can be systematically controlled through network design. Structural characteristics including pore architecture, directional organization, and hierarchical features from nano to macro scales can be precisely engineered. Dynamic behaviors such as self-healing efficiency, stimuli-response rates, and reversible shape changes can also be optimized through careful selection and combination of different molecular design strategies and processing methods. This level of property control enables the development of biopolymer-based hydrogels tailored for specific applications, as demonstrated by the following examples. Recent advances in biopolymer-based hydrogel engineering have demonstrated that a strategic combination of various approaches can further inspire biopolymer-based hydrogels with precisely tailored properties. An enlightening example has been demonstrated by κ-carrageenan/polyacrylamide double network hydrogels reinforced with Zr^{4+} coordination bonds. This approach begins with the formation of a κ-carrageenan (κ-CG) network, which serves as the first network in the double network structure. The κ-CG network is then interpenetrated with a polyacrylamide (PAAm) network, creating a robust double network system. The addition of Zr^{4+} ions introduces metal coordination bonds, further reinforcing the hydrogel structure (**Figure 4a**).[59] This combination of double network formation, metal coordination, and thermo-condensation results in highly transparent hydrogels with remarkable mechanical properties (Figure 4b). The resulting materials exhibit tensile breaking stress up to 3.2 MPa, breaking strain of 2200%, and high-water content (83–91 wt.%), showcasing the synergistic effects of these combined strategies (Figure 4c).

Similarly, another innovative approach involves introducing hydroxypropyl cellulose (HPC) fibers to enhance entanglement and hydrogen bonding within hydrogel systems. This method starts with the incorporation of HPC fibers into the hydrogel matrix (Figure 4d).[54] The presence of these fibers significantly alters the network structure, introducing additional points of entanglement and numerous sites for hydrogen bonding (Figure 4e). As a result, this strategy yields a 10-fold increase in Young's modulus and a 22-fold improvement in toughness compared to hydrogels without HPC reinforcement (Figure 4f). Beyond mechanical enhancement, this method also imparts smart functionalities like faster response times and better resistance to freezing and drying, demonstrating the multifaceted benefits of this combined approach.

Another notable approach involves the creation of bicontinuous hydrogels with distinct subdomains. This strategy utilizes controlled immiscibility between two polymer phases to create a unique network structure (Figure 4g).[60] By carefully selecting and modifying biopolymers, researchers have developed systems where two distinct phases coexist within the hydrogel, each contributing unique properties to the overall material (Figure 4h). This approach has shown particular promise in promoting rapid 3D cell migration, as the distinct subdomains provide both structural support and cell-friendly microenvironments (Figure 4i). The combination of dual-phase structure and biocompatibility makes these hydrogels especially attractive for tissue engineering applications.

Lastly, the development of ionogels with hierarchical non-covalent bonding represents another strategy in combined hydrogel design strategies.[61] This approach leverages multiple types of non-covalent interactions occurring simultaneously, including hydrogen bonding and electrostatic forces, to create a multimodal bonding network (Figure 4j). The resulting materials exhibit a remarkable combination of properties, including extreme stretchability and high toughness (Figure 4k). These ionogels can achieve strains of up to 10250% and toughness values of 21.8 MJ m^{-3}, while still maintaining high ionic conductivity (Figure 4l). The hierarchical nature of the non-covalent bonding allows for efficient energy dissipation and self-recovery, contributing to the material's exceptional mechanical performance.

Each design strategy offers advantages and challenges. For example, double networks provide mechanical robustness but involve complex synthesis, while entanglement systems enhance responsiveness at the cost of some stability. Bicontinuous structures support cellular interactions, though scalability is a concern, and ionogels show remarkable stretchability but may struggle with shape retention. Merging these approaches could lead to

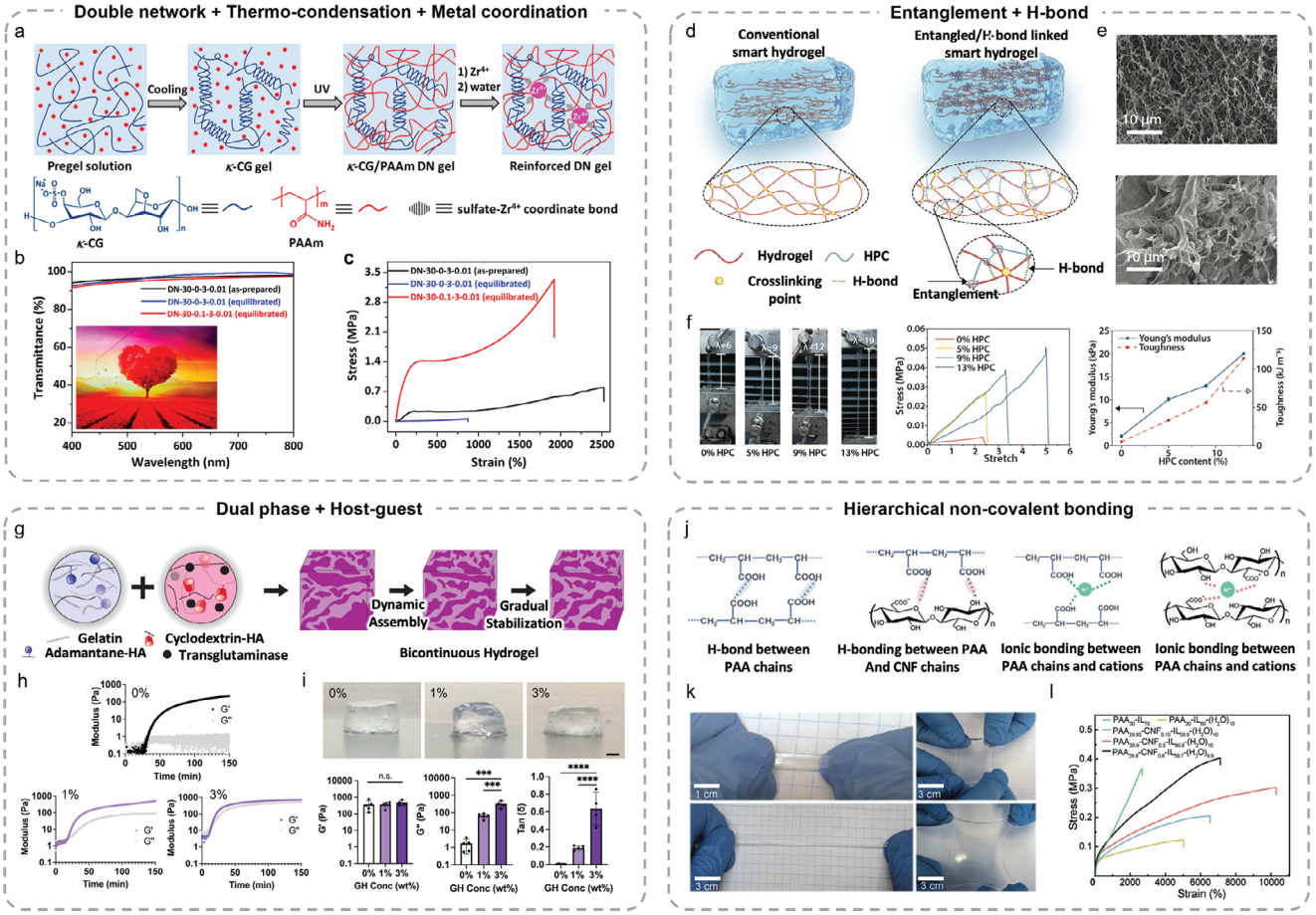

Figure 4. Advanced network design strategies for biopolymer-based hydrogels. a–c) Double network + Thermo-condensation + Metal coordination: a) Schematic of κ-CG/PAAm double network hydrogel formation and Zr^{4+} reinforcement. b) Transmittance spectra of hydrogels. c) Stress–strain curves showing enhanced mechanical properties. Adapted with permission.[59] Copyright 2019 American Chemical Society. d–f) Entanglement + H-bond: d) Illustration of conventional and HPC-entangled hydrogel structures. e) Scanning electron microscopy (SEM) images of HPC fibers in the hydrogel. f) Images and mechanical properties and toughness versus HPC content. Adapted with permission.[54] Copyright 2023 Wiley-VCH. g–i) Dual-phase + Host-guest: g) Formation process of bicontinuous hydrogel from gelatin and hyaluronic acid derivatives. h) Rheological properties of hydrogels with varying compositions. i) Visual appearance and cell migration in hydrogels with different guest-host contents. Adapted with permission.[60] Copyright 2024 Springer Nature. j–l) Hierarchical non-covalent bonding: j) Schematic of hierarchical interactions in cellulose nanofiber-based ionogels. k) Photographs demonstrating the extreme stretchability of ionogels. l) Stress–strain curves of ionogels with varying compositions. Adapted with permission.[61] Copyright 2023 Wiley-VCH.

materials that balance mechanical strength with flexibility, opening new possibilities for tailored hydrogels.

3.2. Processing Strategies for Tailored Biopolymer-based Hydrogel Structures

Beyond network design strategies, processing techniques play a crucial role in tailoring the microscopic structure and properties of biopolymer-based hydrogels. By manipulating factors such as polymer chain organization, pore architecture, and structural anisotropy. As a result, processing strategies can rule key biopolymer-based hydrogel characteristics including their biodegradation profile, viscoelasticity, and responsiveness. Thus, the processing techniques also provide a powerful toolbox for engineering hydrogels with precisely defined properties. Several ingenious processing strategies, including the Hofmeister effect (**Figure 5a**), cononsolvency effect (Figure 5b), and (de)protonation (Figure 5c), have been developed for regulating polymer strand conformation and density, while techniques like mechanical training (Figure 5d) and directional freezing (Figure 5e) have been adopted for creating biopolymer-based hydrogels with bio-mimic orientated alignment.

3.2.1. Hofmeister Effect-Induced Chain Aggregation

The Hofmeister effect leverages the chaotropic and kosmotropic effect of ions on polymer-water interactions to manipulate polymer chain aggregation, allowing for feasibly tuning hydrogel properties without altering their chemical composition (Figure 5a). Luo et al.[62] demonstrated this principle in creating nanocellulosic triboelectric aerogels. By using sodium citrate, a kosmotropic salt, they induced controlled aggregation

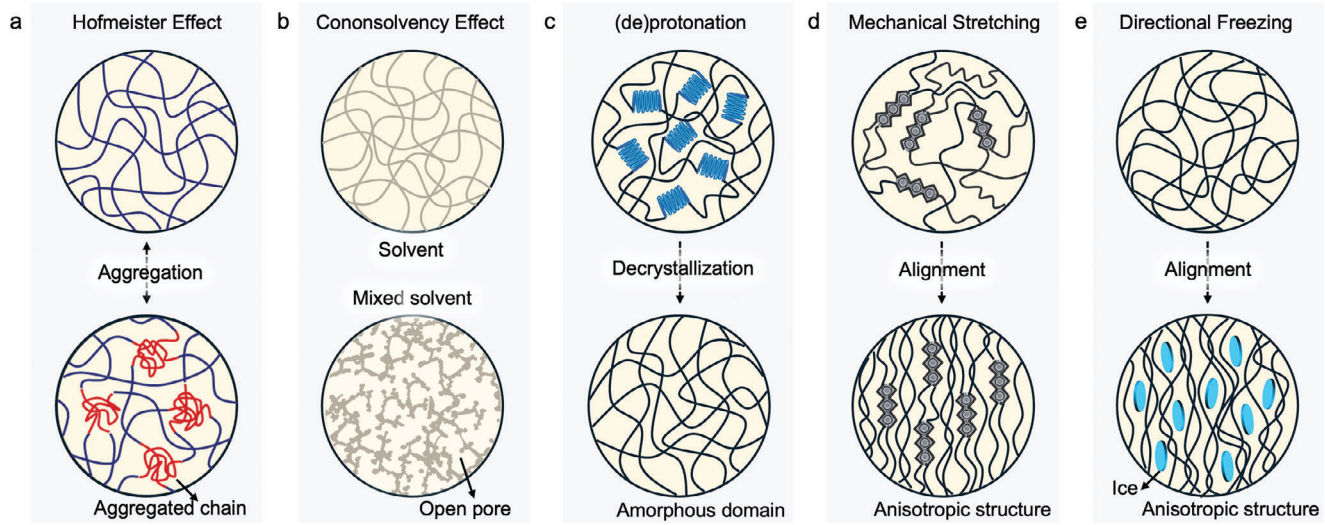

Figure 5. Advanced processing strategies for tailoring biopolymer-based hydrogel structures. a) Hofmeister Effect: Inducing polymer chain aggregation through salt-mediated interactions. b) Cononsolvency Effect: Creating open porous structures using mixed solvent systems. c) Alkali/acid Treating: Generating amorphous domains through decrystallization of ordered regions. d) Mechanical Stretching: Achieving anisotropic structures through the alignment of polymer chains. e) Directional Freezing: Forming aligned anisotropic structures with ice crystal templating.

and crystallization of cellulose nanofibrils (CNFs). The mechanism involves salt ions disrupting the hydration shell around the CNFs, promoting inter-fibril interactions and subsequent aggregation. This process can be visualized as a transition from a "salting-in" state where polymer chains are well-hydrated and dispersed, to a "salting-out" state where chains aggregate and crystallize (**Figure 6a**). This aggregation process results in significant changes to the hydrogel's structure and properties. Experimental evidence of the Hofmeister effect on hydrogel properties shows visible changes in the hydrogel's appearance and mechanical properties as salt concentration increases (Figure 6b). Quantitative analysis reveals increases in compression ratio, toughness, and modulus correlating with rising salt concentration.

At the microscale, these property changes are reflected in the hydrogel's internal architecture. Microscopy images reveal the evolution of the hydrogel's structure with increasing salt concentration, from a relatively loose structure at low concentrations (0.5 M) to a more compact and interconnected network at higher concentrations (1.0 and 1.5 M), explaining the enhanced mechanical properties (Figure 6c). This process resulted in aerogels with Young's modulus of 142.9 MPa and a specific modulus of 340.6 kN m kg^{-1}, showcasing how ion-induced structuring can dramatically enhance mechanical properties.

3.2.2. Cononsolvency-Based Pore Structure Control

The cononsolvency effect, while less explored in biopolymer systems, offers significant potential for controlling hydrogel structure and properties (Figure 5b). Alsaid et al.[63] demonstrated the power of this effect in creating hydrogels with hierarchical open pore structures. Although their work primarily focused on synthetic polymers like poly(N-isopropylacrylamide) (PNIPAM), the underlying principles are applicable to biopolymer systems. Polymer conformation changes in mixed solvent systems at different temperatures and solvent ratios can be understood through a phase diagram showing three distinct regions: "Coil" where polymer chains are extended, "Globule" where chains collapse, and a two-phase region (Figure 6d). By utilizing mixed solvent systems of water and dimethyl sulfoxide (DMSO), they induced a coil-to-globule transition in the polymer chains during gelation. This transition leads to the formation of interconnected microporous structures within the hydrogel. The mechanism involves localized phase separation driven by preferential interactions between the polymer and different solvent components. SEM images reveal the evolution of porous structures formed at different solvent ratios. As the ratio of DMSO to water changes, the pore structure evolves from a relatively dense network to increasingly open and interconnected structures (Figure 6e).

Notably, at DMSO fraction = 0.5, a bimodal pore size distribution emerges, with micropores (1–10 μm) coexisting with macropores (30–50 μm). This hierarchical porosity resulted in a 215% increase in water uptake capacity compared to the homogeneous hydrogel, rising from 450% to 1417% relative to the dry weight. This demonstrates how precise control over solvent composition can be used to tailor hydrogel porosity. In biopolymer systems, this approach could be adapted to create hydrogels with controlled porosity, potentially enhancing properties such as swelling capacity, mechanical strength, and diffusion rates.

3.2.3. (De)protonation for Crystallinity Modification

Alkali or acid treatments offer another convenient means to manipulate the crystallinity of biopolymers, which is particularly useful for cellulose-based materials, by disrupting hydrogen bonding within ordered regions to create more amorphous, flexible structures (Figure 5c). Ghasemi et al.[64] elucidated the mechanisms underlying this process in their comprehensive study on cellulose dissolution. The cellulose processing steps involve

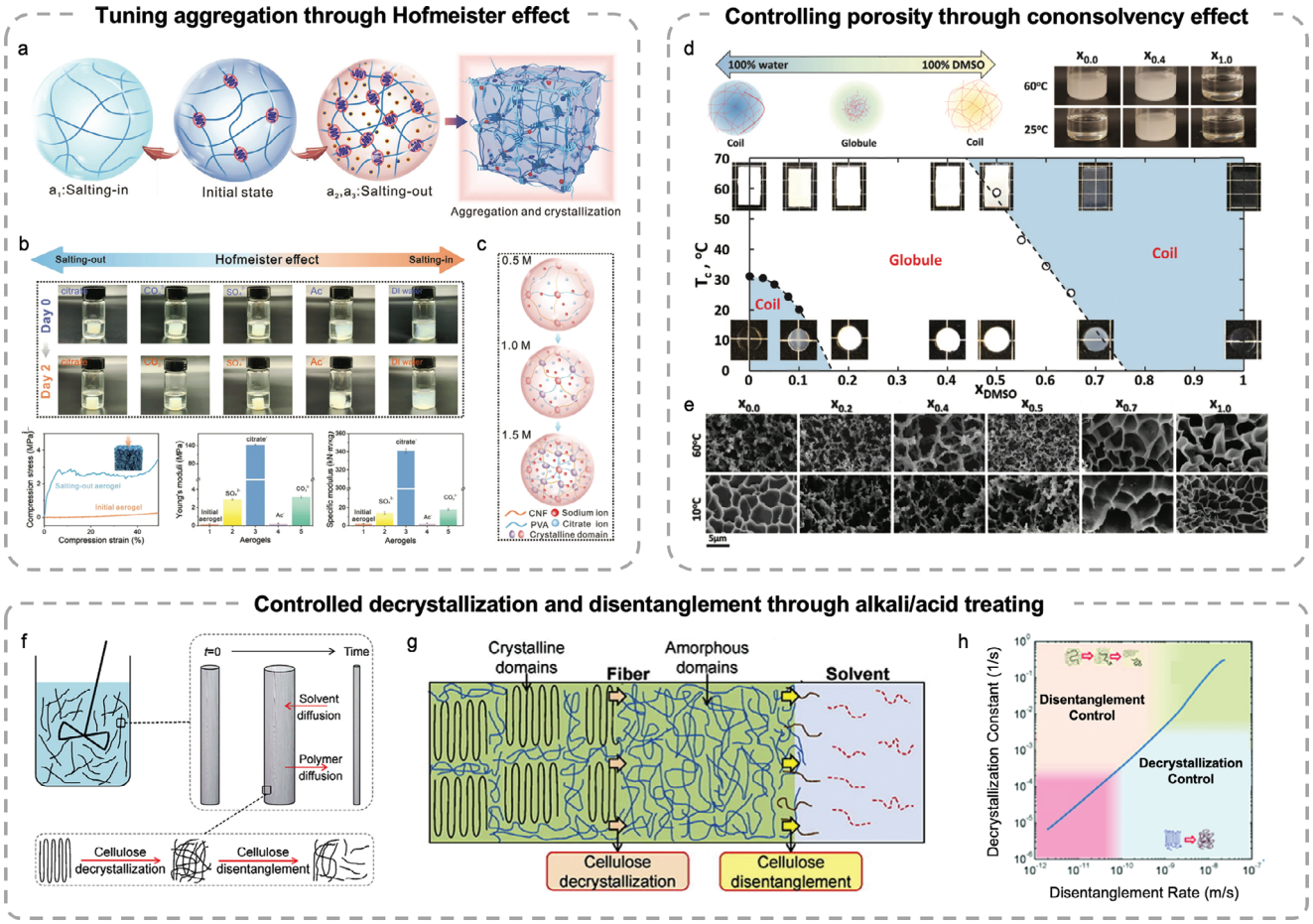

Figure 6. Advanced processing strategies for tailoring biopolymer-based hydrogel structures. a–c) Tuning aggregation through Hofmeister effect: a) Schematic showing biopolymer chain aggregation induced by salting-out ions. b)Experimental demonstration of Hofmeister effect on hydrogel properties with increasing salt concentration. c) Microscale changes in hydrogel structure with salt treatment. Adapted with permission.[62] Copyright 2023 Wiley-VCH. d,e) Controlling porosity through solvent-induced phase separation: d) Phase diagram illustrating polymer conformation changes in mixed solvent systems at different temperatures. e) SEM images reveal porous structures formed at different solvent ratios. Adapted with permission[63] Copyright 2021 Wiley-VCH. f–h) Controlled decrystallization and disentanglement through alkali/acid treating: f) Illustration of cellulose processing steps. g) Schematic of structural changes in cellulose fibers during treatment. h) Plot showing the relationship between decrystallization and disentanglement rates for different cellulose solvents. Adapted with permission.[64] Copyright 2017 Elsevier.

solvent diffusion into the polymer matrix leading to polymer chain dissolution (Figure 6f). They identified two rate-limiting steps: decrystallization, where alkali disrupts hydrogen bonds within crystalline regions, and disentanglement, where individual cellulose chains separate from each other. The structural changes in cellulose fibers during treatment show the transition from crystalline domains to amorphous regions as the solvent penetrates and disrupts the hydrogen bonding network (Figure 6g). The balance between these processes depends on solvent characteristics such as pH and ionic strength. The relationship between decrystallization and disentanglement rates for different cellulose solvents can be visualized in a plot divided into four regions (A, B, C, D) representing different rate-limiting scenarios (Figure 6h). For example, in certain alkali solutions (region B), decrystallization occurs rapidly, but disentanglement becomes the limiting factor. This control over crystallinity and chain entanglement directly influenced mechanical properties. Decreasing crystallinity from 68% to 40% resulted in a substantial reduction in tensile strength but an increase in elongation at break, demonstrating how (de)protonation can be used to tailor cellulose-based hydrogel properties.

Overall, the Hofmeister effect and (de)protonation method provide a bottom-up method for tailoring polymer-polymer and polymer-solvent interactions by introducing certain third parties to control the polymer aggregation. They offer a timely and powerful method for optimizing overall hydrogel performances to fit applications ranging from drug delivery to tissue engineering scaffolds. The material property could also be macroscopically regulated by top-down manipulation. Complex architectures of natural tissues, such as directional aligned muscle, gradient distributed porous plant petiole, and layer-by-layer (LBL) chameleon skin, have been proved to the merit for their outstanding performances. By replicating these hierarchical structures, biopolymer-based hydrogels can better recapitulate and surpass the mechanical and biological functions of natural systems.

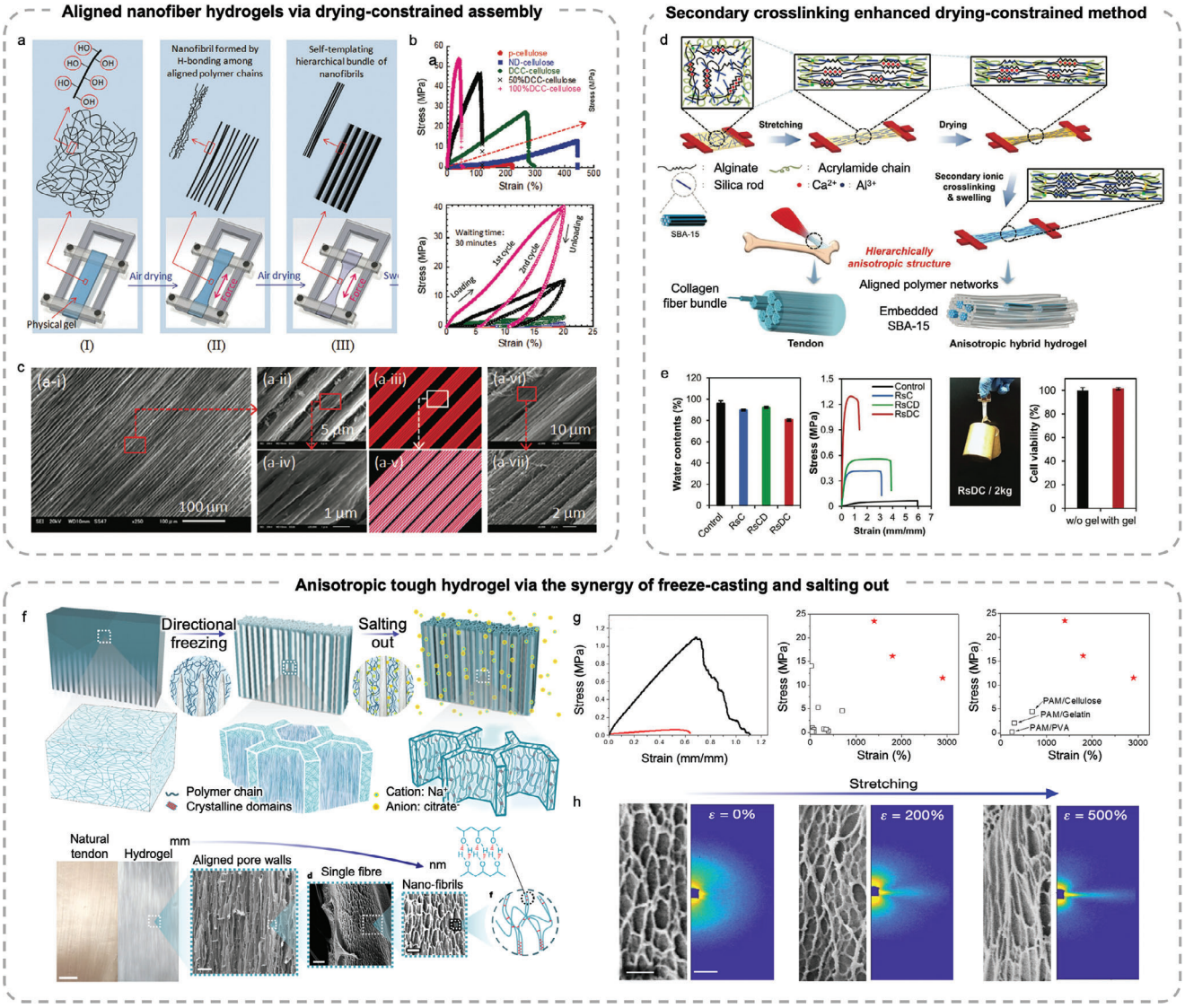

Figure 7. Strategies for creating anisotropic biopolymer-based hydrogels. a–c) Aligned nanofiber hydrogels via drying-constrained assembly: a) Schematic showing physical gel formation, nanofibrillation, and self-organizing reassembly. b) Stress–strain curves demonstrating mechanical anisotropy with different water contents and loading directions. c) SEM images showing aligned fibrous structures at multiple scales (scale bars: 100, 1, and 10 µm). Adapted with permission.[65] Copyright 2018 Wiley-VCH. d,e) Secondary cross–linking enhanced drying-constrained method: d) Illustration of the process combining stretching, drying, and ionic cross–linking. e) Water content, mechanical properties, and cell viability in the resulting anisotropic hydrogels. Adapted with permission.[66] Copyright 2019 Wiley-VCH. f–h) Anisotropic tough hydrogel via the synergy of freeze-casting and salting out: f) Schematic of the fabrication process combining directional freezing and salt-induced polymer aggregation. g) Stress–strain curves demonstrating mechanical anisotropy (left) and mechanical properties of HA-PVA hydrogel compared to those of PVA hydrogels prepared by ice-templating alone (middle) or salting out alone (right). h) SEM images and stress distribution maps showing structural changes during stretching. Adapted with permission.[67] Copyright 2021 Springer Nature.

3.2.4. Mechanical Training for Anisotropic Structures

Like the biceps can get trained to be more orientated and stronger by repeated lifting workouts, the mechanical training techniques that cyclically tensile and recover the biopolymer-based hydrogels could also induce alignment of polymer chains to create an anisotropy biopolymer-based hydrogels (Figure 5d). Mredha et al.[65] developed a facile method called "drying in confined condition" (DCC) to fabricate anisotropic hydrogels with highly aligned, hierarchical fibrous structures. The DCC process involves three key steps (**Figure** 7a): I) physical gel formation, II) nanofibrillation by shearing along the longitudinal axis, and (III) self-organizing reassembly of nanofibrils. This approach, applied to alginate and cellulose hydrogels, resulted in materials with mechanical properties comparable to natural ligaments, including Young's moduli up to 367 MPa for alginate and 342 MPa for cellulose. The stress–strain curves (Figure 7b) clearly demonstrate the mechanical anisotropy of the resulting hydrogels, with significantly higher strength and modulus in the aligned direction compared to the perpendicular direction. SEM images reveal

the hierarchical structure of the aligned nanofibers at different scales (Figure 7c). The images show highly oriented fibers at the microscale (100 μm), which maintain their alignment down to the nanoscale (1 μm), confirming the effectiveness of the DCC method in creating multi-scale anisotropic structures.

Building on this concept, Choi et al.[66] introduced an enhanced approach for creating anisotropic hybrid hydrogels reminiscent of tendons or ligaments. Their method combines stretching, drying, and ionic cross–linking of alginate-polyacrylamide double network hydrogels with rod-shaped mesoporous silica microparticles (Figure 7d). This secondary cross–linking enhanced DCC method involves stretching the hydrogel, allowing it to dry in the stretched state, and then introducing ionic cross–links to stabilize the aligned structure. The resulting hydrogels exhibited remarkable mechanical properties, with a tensile modulus of 7.2 MPa, strength of 1.3 MPa, and toughness of 1.4 MJ m^{-3}, while maintaining a high-water content of 81% (Figure 7e).

3.2.5. Directional Freezing for Aligned Networks

Besides mechanical training, directional freezing is another method for creating directional alignments in biopolymer-based hydrogels that employ controlled ice crystal growth to template-aligned porous structures, offering a route to create materials with anisotropic properties and enhanced diffusion characteristics (Figure 5e). Building upon directionally, another powerful approach combines freeze-casting with salting out, as demonstrated by Hua and coworkers.[67] By leveraging the synergy of directional freezing and salt-induced polymer aggregation, they created hydrogels with aligned porous structures and enhanced mechanical properties. The fabrication process (Figure 7f) involves directional freezing of a polymer solution containing salt, followed by a freeze-drying step to create the initial porous structure. Subsequent salt-induced aggregation further enhances the mechanical properties of the aligned structure.

While their work primarily focused on poly(vinyl alcohol) (PVA), they also applied this technique to biopolymers, notably gelatin and alginate, showcasing the effectiveness of such a method for natural polymer systems. For alginate hydrogels prepared using this method, they observed a significant increase in mechanical anisotropy, with the compressive strength in the freezing direction reaching up to 0.5 MPa, nearly double that in the perpendicular direction. The stress–strain curves (Figure 7g) clearly demonstrate the mechanical anisotropy achieved through this method, with the aligned direction showing higher strength and toughness compared to the perpendicular direction. SEM images and stress distribution maps (Figure 7h) reveal how the aligned porous structure changes during stretching, providing insight into the mechanism of enhanced mechanical properties. This approach offers several advantages for biopolymer-based hydrogel engineering. First, it allows for fine-tuning of the hydrogel structure and properties by adjusting freezing conditions (e.g., cooling rate, temperature gradient) and salt concentrations. Second, it enables the creation of complex, anisotropic structures without the need for external mechanical forces, making it suitable for a wide range of biopolymer-based hydrogels. Third, the resulting aligned porous structures can be useful for guiding cell growth and tissue formation, making this method favorable for creating biopolymer-based hydrogels for biomedical applications.

Each processing strategy presents distinct advantages and limitations for practical implementation. The Hofmeister effect offers precise control over mechanical properties through simple salt treatment but may face challenges in maintaining uniform ion distribution in large samples. Cononsolvency-based approaches enable the creation of controlled porous structures but require careful solvent selection to maintain biocompatibility. (De)protonation methods provide rapid property modulation but may affect the biological functionality of sensitive biopolymers. Mechanical training produces strong anisotropic structures but faces scalability challenges for mass production. Directional freezing enables the creation of aligned structures with good scalability, though careful temperature control is needed to ensure uniformity in larger samples. Understanding these trade-offs is crucial for selecting appropriate processing strategies based on specific application requirements. For instance, while both the Hofmeister effect and directional freezing can enhance mechanical properties, the former may be more suitable for small biomedical devices requiring precise property control, while the latter could be better adapted for larger tissue engineering scaffolds needing consistent internal architecture.

As summarized above, both network design strategies and processing techniques are feasible but powerful tools for customizing biopolymer-based hydrogel properties. It can be imagined that the synergy between molecular/network design and processing techniques will allow researchers to overcome limitations inherent to specific biopolymers, expanding the range of achievable material properties and opening new avenues to realizing the full potential of biopolymer-based hydrogels for application-specific hydrogel development.

4. Structure-Property Theories

The intricate relationship between molecular structure and macroscopic properties forms the cornerstone of rational biopolymer-based hydrogel design.[4a] Versatile designing and processing methods require theoretical guidance to tailor the biopolymer-based hydrogels for real demands.[68] This section elucidates theoretical models of important biopolymer-based hydrogel properties, including stiffness, stress relaxation, mass exchange/transportation, and degradation, that are highly valued in actual applications. With detailed comprehension of these structural parameter-material property relationships, researchers can strategically design and manipulate biopolymer-based hydrogels for specific uses and optimize performance across scales.

4.1. Mechanical Behavior

The mechanical behavior of biopolymer-based hydrogels, as illustrated in **Figure 8**a,b, exemplifies how molecular-level design choices manifest in macroscopic material properties. Figure 8a shows a typical tensile strain curve of biopolymer-based hydrogels, which is featured by distinct regimes that reflect the hierarchical nature of hydrogel structures: i) A linear elastic region at low strains, where behavior is dominated by cross–link

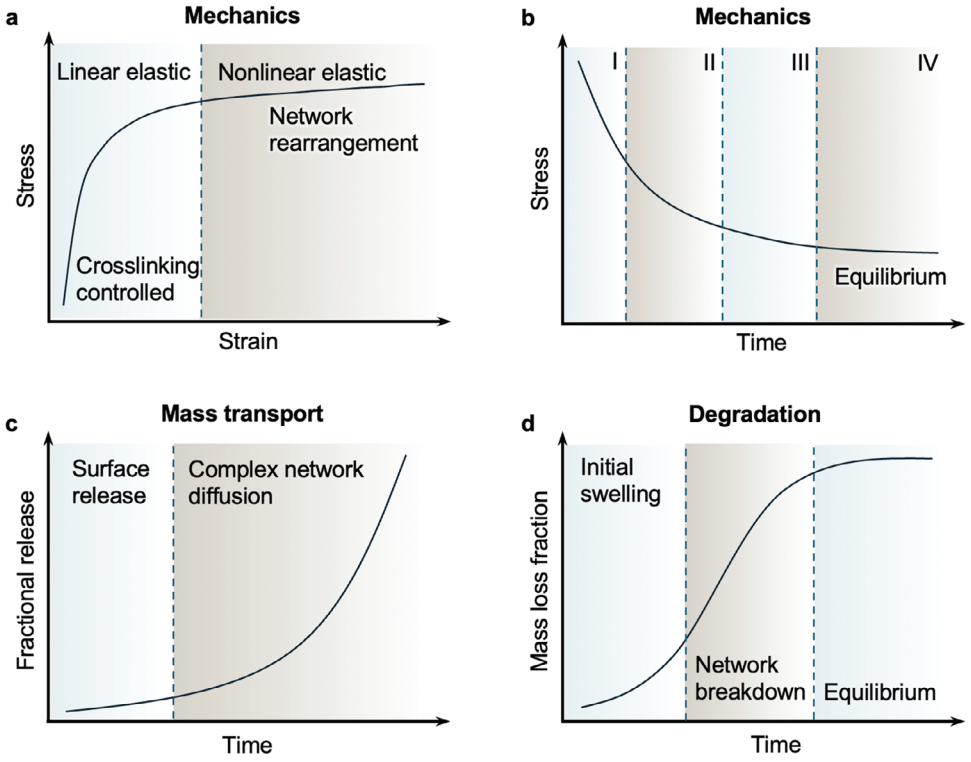

Figure 8. Fundamental structure-property relationships in biopolymer-based hydrogels. a) Stress–strain response illustrating the transition from linear elasticity governed by cross–link deformation to nonlinear behavior dominated by network rearrangement. b) Multi-stage stress relaxation curve revealing distinct relaxation mechanisms across different timescales. c) Biphasic mass transport kinetics showing initial surface-mediated release followed by network-controlled diffusion. d) Degradation profile demonstrating the progression from initial swelling through network breakdown to equilibrium state.

deformation and entropic elasticity of polymer chains; ii) A nonlinear elastic region at higher strains are characterized by significant network rearrangement, such as the unfolding and sliding of polymer segments.

In the linear elastic regime, the stress–strain relationship is given by Hooke's law:[69]

$$\sigma = E\epsilon \tag{1}$$

where σ is stress, ϵ is strain, and E is the elastic modulus. For biopolymer-based hydrogels, E can be approximated using rubber elasticity theory:

$$E \approx 3\rho_x kT \tag{2}$$

Here, ρ_x is the cross–link density, k is the Boltzmann constant, and T is the temperature. This relationship directly connects molecular-level cross–linking features to macroscopic material stiffness. The range of elastic region is decided by biopolymer chain length and cross–link density when the stiffness of biopolymer-based hydrogels are mostly rate-dependent as they are abundant in dynamic bonds. At low strain rates, the dynamic bonds have little contribution to the modulus due to sufficient time for their relaxation. Thus, the hydrogel behaves as a soft solid with stiffness purely contributed by elastic stands. At high strain rates, the dynamic bonds play a similar role to the permanent cross–linking, and the hydrogel behaves as a hard elastic solid with a large stiffness.[16b]

As strain increases, hydrogels transition to a nonlinear regime, a visco-hyperelastic model combining Gent hyperelasticity with time-dependent modulus evolution better captures this behavior:[70]

$$\sigma = \mu \frac{\lambda^2 - \lambda^{-1}}{1 - \left(\lambda^2 + 2\lambda^{-1} - 3\right)/J_m} + \int_0^t G\left(t - \tau\right) \frac{d\epsilon}{d\tau} d\tau \tag{3}$$

where $G\left(t\right) = G_0\ e^{-(t/\tau)^\beta}$ (stretched exponential function) describes the time-dependent modulus decay due to bond dissociation. This model effectively captures the stress plateau characteristic of biopolymer hydrogels under large deformation, which results from extensive network reorganization. The material response is inherently rate-dependent due to the presence of dynamic bonds. Under low strain rates, these dynamic bonds contribute minimally to the modulus as they have sufficient time for relaxation, causing the hydrogel to behave as a soft solid with properties dominated by permanent elastic strands. Conversely, at high strain rates, the dynamic bonds function similarly to permanent cross–links, resulting in a stiffer material response.[16b] The nonlinear response arises from complex molecular processes including physical cross–link dissociation, chain disentanglement, and the formation of the new temporary cross–links. This network rearrangement mechanism fundamentally differs from traditional strain hardening, providing biopolymer

hydrogels with their characteristic mechanical properties and enabling their adaptability to large deformations.

Due to the inherent viscosity of biopolymers, stress relaxation is a prominent feature in biopolymer-based hydrogels. Understanding this unique behavior enables more accurate predictions of biopolymer-based hydrogels post-treatment evolution, paving the way for designing controllable drug delivery systems, self-deploying implants, programmable actuators, soft robots, etc. The stress relaxation behavior of biopolymer-based hydrogel (Figure 8b).[71] To capture the multi-timescale relaxation dynamics, a fractional Zener model is more appropriate:

$$\sigma(t) + \tau^{\alpha} \frac{d^{\alpha}\sigma}{dt^{\alpha}} = E_{\infty}\,\epsilon + E_0 \tau^{\beta} \frac{d^{\beta}\epsilon}{dt^{\beta}} \tag{4}$$

where E_0 and E_∞ represent the instantaneous and equilibrium moduli, respectively, and α, β are fractional exponents governing the power-law relaxation spectrum. This model successfully describes the stress decay in physically cross–linked hydrogels (e.g., gelatin, agarose) by accounting for the broad distribution of bond lifetimes, each corresponding to specific molecular mechanisms (Figure 8b). Stage I involves rapid reorganization of water molecules and local polymer chain segments, causing an initial sharp decrease in stress. In Stage II, polymer chains undergo more extensive reorganization while maintaining network connectivity. Stage III is characterized by slower relaxation processes involving the breaking and reformation of physical cross–links, while permanent cross–links maintain the network structure. Finally, in Stage IV, the system reaches an equilibrium state where the stress stabilizes at a finite value determined by the permanent network structure.

The relaxation profile can be tailored through molecular design and processing strategies. The permanent network contribution (E) is controlled by chemical cross–link density, while the viscous response (η) depends on chain flexibility, physical cross–link dynamics, and network architecture. Higher cross–link density increases the equilibrium stress, while stronger physical interactions extend relaxation times. Moreover, hierarchical structures created through directional freezing or controlled phase separation can introduce multiple relaxation timescales, enabling more complex and controllable relaxation behaviors. This nonzero equilibrium stress is crucial for many applications, particularly where mechanical stability is required over extended periods. By strategically manipulating network architecture and cross–linking chemistry, researchers can engineer biopolymer-based hydrogels with precisely controlled relaxation profiles while maintaining desired long-term mechanical properties.

4.2. Mass Transportation

The continuous inner water phase allows smooth mass exchange between biopolymer-based hydrogels and the external environment. The interfacial mass transport behavior in biopolymer-based hydrogels is fundamental to its stimuli-responsiveness and applications such as drug delivery and tissue engineering, tissue scaffolding, etc. The typical release profile of biopolymer-based hydrogels is illustrated in Figure 8c distinguishable from diffusion between two liquids that are decided by concentration mismatch, the diffusion of biopolymer-based hydrogels exhibits two distinct phases: an initial burst release followed by a sustained, network-controlled diffusion. Such biphasic behavior can be described by the Korsmeyer-Peppas model:[70b,72]

$$\frac{M_t}{M_\infty} = k t_d^{n} \tag{5}$$

where M_t/M_∞ is the fractional release at time t, k is a rate constant, and n is the release exponent. The value of n indicates various release mechanisms: $n \leq 0.45$ suggests Fickian diffusion, also known as Case I transport, which refers to the solute transport process in which the polymer relaxation time (t_r) is much greater than the characteristic solvent diffusion time (t_d); $0.45 < n < 0.89$ indicates non-Fickian transport, which corresponds to the case that $t_r \approx t_d$; and $n \geq 0.89$ represents Case II transport, where polymer network influence to diffusion is neglectable. The initial burst release (usually $n < 0.45$) is primarily governed by surface and near-surface matter dissolution, while the sustained release phase is controlled by diffusion inside the hydrogel network.[73] The Ogston model indicates that the diffusion coefficient (D) within the network is related to the mesh size (ξ):

$$\frac{D}{D_0} = \exp\left(-\frac{\pi}{4}\frac{r_f + r_s}{\xi}\right) \tag{6}$$

Here, D_0 is the diffusion coefficient in water, r_f is the fiber radius, and r_s is the solute radius. Such knowledge provides clear guidance for tailoring absorbing and releasing kinetics by rational structural design for desired functionalities. Pores size and tortuosity would severely affect the mass transportation inside the biopolymer-based hydrogels, as they contribute to the r_f and D_0, respectively. Techniques like directional freezing and phase separation have been used to create continuous or aligned channels in biopolymer-based hydrogels, enabling fast mass transport. Beyond this, other customized transport or release behaviors can be achieved through rational structural design. For example, gradient mesh sizes have been shown to enable sustained, long-lasting inner-to-outer mass exchange.

4.3. Degradation

The degradation behavior of biopolymer-based hydrogels, as illustrated in Figure 8d, is also critical for designing highly stable or on-demand degradable biopolymer-based hydrogels. The degradation profile of biopolymer-based hydrogels typically exhibits three distinct stages: initial swelling, network breakdown, and equilibrium.[74] The initial swelling phase is predominantly controlled by the hydrogel's hydrophilicity and cross–link density. The network breakdown phase is governed by the nature of cross–links and the accessibility of degradable bonds. Strategies to control the network breakdown phase include: i) Enzyme-responsive linkages: Incorporating specific peptide sequences that are cleavable by target enzymes allows for site-specific degradation; ii) Hydrolytically degradable bonds: Using ester or anhydride linkages enables hydrolysis-driven breakdown, with degradation rates tunable through bond chemistry; iii) Stimuli-responsive degradation, physical and chemical stimuli can trigger controlled network breakdown if corresponding responsive

units have been embedded biopolymer-based hydrogel matrix. This approach allows for on-demand degradation in response to specific environmental cues. The equilibrium stage is the final stage when the degradation rate balances with the remaining network structure. Engineering this stage involves: i) Incorporation of non-degradable components: by integrating stable polymer segments or nanoparticles, a residual network can be maintained even after extensive degradation; ii) Hierarchical structures: creating multi-layered or gradient structures, as demonstrated in the directional freezing techniques discussed earlier, allows for differential degradation rates across the hydrogel. This approach can lead to sustained, controlled degradation profiles over extended periods.

These mechanical models also predict how physiological conditions affect hydrogel behavior. Under physiological variations, the modulus and relaxation characteristics undergo significant changes. For example, increased temperature (e.g., from room temperature to 37 °C) typically accelerates stress relaxation by reducing τ_i values through enhanced chain mobility. pH changes can dramatically impact network properties – acidic conditions often strengthen hydrogen bonding and ionic interactions, while basic conditions may weaken them, shifting both E and J_m. Additionally, the presence of ions at physiological concentrations (e.g., Na^+, K^+, Ca^{2+}) can screen electrostatic interactions and alter cross–link density, affecting mechanical response across all deformation regimes. Understanding these environment-dependent behaviors is crucial for predicting hydrogel performance in biomedical applications such as tissue scaffolds, drug delivery systems, and implants.

5. Large-scale Fabrication Methods for Complex Structures

The sophisticated network design strategies and processing techniques discussed thus far lay a strong foundation for engineering biopolymer-based hydrogels with tailored properties.[75] However, bridging the gap between molecular-scale design and macroscopic, functional structures demands equally advanced fabrication techniques.[76] These techniques must not only preserve the intricate molecular architecture but also precisely control the spatial organization of different components across multiple length scales. Recent advances in fabrication methods have significantly expanded our ability to create complex, biomimetic hydrogel structures that closely mimic the intricate architectures found in natural tissues.[77] This section explores fabrication approaches that exemplify the current methods in biopolymer-based hydrogel engineering. These techniques collectively enable unprecedented control over hydrogel composition, architecture, and functionality.

For instance, eluting mold casting has emerged as a powerful method for creating complex, multi-layered hydrogel structures at human scale. This approach, demonstrated by Tosoratti et al.,[78] represents a significant leap forward in our ability to fabricate tissue-mimetic constructs (**Figure 9a**). By employing computationally optimized "metamolds" and controlled diffusion of cross–linking agents, this technique achieves remarkable resolution and shape fidelity while being scalable to clinically relevant sizes. The successful creation of a two-layered, human-sized ear construct with distinct cartilage and vascularized dermal components illustrates the potential of this method to revolutionize the field of tissue engineering. This achievement not only showcases the versatility of biopolymer-based hydrogels but also highlights how advanced fabrication techniques can unlock their full potential in creating functional, multi-tissue structures.

The progress of 3D printing techniques for biopolymer-based hydrogels has opened new strategies for creating structures with unprecedented spatial control over material properties and cellular environments. Embedded 3D printing, as demonstrated by de Melo et al.,[79] represents a significant advancement in this field (Figure 9b). By combining mechanically robust interpenetrating networks with soft, cell-friendly microenvironments, this approach bridges the gap between structural integrity and biological functionality. The ability to create cartilage-like constructs with moduli matching native tissue while maintaining optimal conditions for cell viability and differentiation showcases the potential of this technique to revolutionize tissue engineering. Another is the use of sustainable, naturally-derived materials in 3D printing, as illustrated by Chen et al.'s work with pollen-based bioinks (Figure 9c).[80] This approach not only addresses the growing need for eco-friendly biomaterials but also introduces new functionalities that are inherent to these natural structures. The transformation of pollen into versatile microgel particles demonstrates how biopolymer processing can unlock hidden potentials in abundant natural resources. The dual functionality of these materials as both reinforcing agents and support matrices for freeform printing highlights the multifaceted nature of biopolymer-based hydrogels. Moreover, the incorporation of stimulus-responsive properties and enhanced cell compatibility into these bioinks showcases how biopolymer-based materials can surpass synthetic alternatives in terms of both functionality and biocompatibility.

The creation of hydrogel-based organ models with complex internal structures represents a frontier in biopolymer fabrication. Jiang et al.[81] have made significant strides in this direction by developing a method that combines 3D printing of thermal splitting hydrogel templates with metal ion-induced interfacial assembly (Figure 9d). This approach leverages the unique properties of a gelatin/ι-carrageenan blend to create intricate internal channels and cavity structures within hydrogels. The technique's ability to produce hollow structures that can withstand physiological pressures (up to 0.11 MPa) demonstrates its potential for creating functional vascular models and other organ-mimetic structures. By using diffusion-induced gelation and controlled template removal, this technique allows for the precise patterning of internal structures that would be challenging or impossible to achieve through conventional molding or 3D printing alone. Furthermore, the ability to create gradient structures through sequential assembly of different hydrogel layers offers a powerful tool for replicating the heterogeneous compositions found in natural organs.

This fabrication technique, along with the embedded 3D printing and pollen-based bioink approaches discussed earlier, exemplifies the current state-of-the-art in biopolymer-based hydrogel engineering. Each of these methods addresses specific challenges in creating biomimetic structures: 1) Eluting mold casting enables the creation of large-scale, multi-layered tissues with high shape fidelity; 2) Embedded 3D printing allows for precise

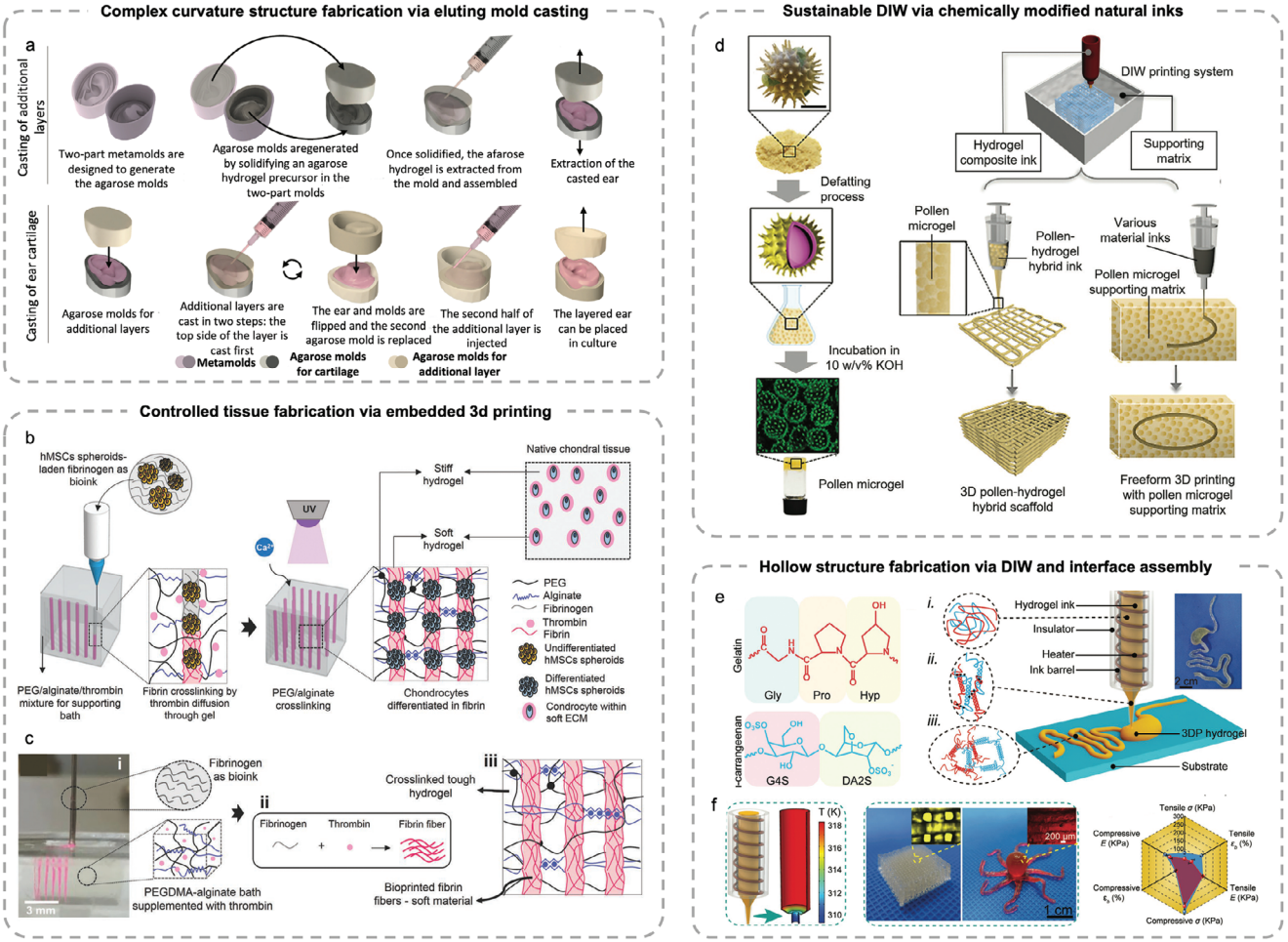

Figure 9. Advanced fabrication techniques for biopolymer-based hydrogels. a) Eluting mold casting: Human-sized ear construct with cartilage core and vascularized dermal layer. Adapted with permission.[78] Copyright 2023 Wiley-VCH. b) Embedded 3D printing: Cartilage-like constructs with spatially controlled mechanical properties. Adapted with permission.[79] Copyright 2019 Wiley-VCH. c) Sustainable direct ink writing: Pollen microgel suspensions used as bioink reinforcement and supporting matrix. Adapted with permission.[80] Copyright 2021 Wiley-VCH. d) Hollow structure fabrication: Organ model with internal channels created via thermal splitting templates and interfacial assembly. Adapted with permission.[81] Copyright 2022 Wiley-VCH.

control over local mechanical properties and cell distribution; 3) Pollen-based bioinks introduce sustainable, multifunctional materials with inherent bioactivity; 4) The thermal splitting template method facilitates the formation of complex internal architectures. Together, these fabrication techniques provide a comprehensive toolkit for translating molecular-level design principles into functional, organ-scale structures.

While these fabrication techniques demonstrate powerful capabilities, several key limitations remain to be addressed. Eluting mold casting, though enabling the creation of large-scale structures, faces challenges in achieving sub-millimeter resolution for intricate internal features and requires optimization of diffusion kinetics for different biopolymer combinations. Embedded 3D printing, while offering excellent spatial control, is currently limited by printing speed (typically <10 mm s^{-1}), material viscosity constraints (0.1–100 Pa s), and challenges in maintaining cell viability during extended printing sessions. Sustainable direct ink writing using materials like pollen faces limitations in ink formulation consistency and mechanical property control. The creation of hollow structures through thermal splitting templates, though promising, requires a careful balance of gelation and template removal kinetics to prevent structure collapse. Additionally, all these techniques face common challenges in maintaining shape fidelity during cross–linking and preventing deformation during media exchange. Future developments should focus on improving resolution while maintaining fabrication speed, expanding compatible material selections, and developing standardized protocols for quality control and scalable production.

6. Applications

The molecular engineering strategies, processing techniques, and fabrication methods discussed in previous sections have enabled unprecedented control over structure and properties across multiple scales for the creation of biopolymer-based hydrogels with advantageous properties and functionalities. These advancements have paved the way for innovative applications that leverage the unique characteristics of biopolymer-based hydrogels,

such as biocompatibility, tunable mechanics, and responsiveness to environmental stimuli. This section explores how the fundamental design principles and fabrication techniques translate into functional materials that address critical challenges in biomedicine, environmental science, and advanced technologies.

6.1. Biomedical Applications

Advancing the molecular design principles of biopolymer-based hydrogels has led to innovative solutions in topical drug delivery, addressing the longstanding challenge of enhancing skin permeation without compromising biocompatibility or mechanical properties. The development of thermoresponsive elastomeric protein eutectogels exemplifies how the strategic combination of materials can yield synergistic benefits. By integrating gelatin and tannic acid within a choline-geranic acid deep eutectic solvent, Picchio et al.[82] have created a system that marries the permeation enhancement capabilities of CAGE with the structural integrity of protein networks (**Figure 10a**). This approach leverages the Hofmeister effect-induced aggregation discussed earlier to achieve remarkable mechanical properties, including high stretchability and toughness, crucial for maintaining contact with the dynamic skin surface. The resulting hydrogels demonstrate how precise control over network formation and stimuli-responsiveness can be harnessed to create materials with multifaceted functionality. The thermoresponsive behavior, likely arising from the temperature-dependent interactions between gelatin chains and the deep eutectic solvent, enables temperature-modulated drug release. This feature, combined with enhanced skin penetration and strong adhesion properties, showcases the potential of tailored biopolymer-based hydrogels to improve topical drug delivery.

The strategies discussed earlier have found compelling applications in addressing the multifaceted challenges of chronic wound healing. By leveraging the versatility of biopolymer-based hydrogels, researchers have developed sophisticated systems that respond dynamically to the complex wound environment. Geng et al.'s multifunctional hydrogel exemplifies how careful selection and modification of biopolymers can yield materials with an array of beneficial properties tailored to wound healing (Figure 10b).[83] This hydrogel system, composed of modified gelatin and oxidized alginate, showcases the pH-responsive degradation likely stems from the integration of dynamic covalent bonds, allowing the hydrogel to adapt to the acidic milieu of chronic wounds. Temperature-dependent adhesion and detachment properties demonstrate the successful implementation of thermo-responsive elements within the network, addressing the critical need for easy dressing changes without causing further trauma. The incorporation of deoxyribonuclease I and indocyanine green into the hydrogel matrix illustrates how biopolymer networks can be engineered to serve as multifunctional delivery vehicles. The observed in vivo efficacy in promoting wound closure, collagen deposition, and angiogenesis underscores the importance of creating biomimetic environments that can interact productively with host tissues.

The molecular engineering principles and processing strategies explored earlier converge in the development of injectable hydrogels, exemplifying their potential in minimally invasive tissue engineering. Zhou et al.'s work[84] on self-healing hydrogel adhesives demonstrates how tailored biopolymer modifications can yield materials with dynamic, multifunctional properties ideal for surgical applications (Figure 10c). This system, based on oxidized chondroitin sulfate and gelatin, showcases the power of combining multiple network design strategies. The pH-responsive gelation leverages dynamic covalent chemistry, enabling precise control over the sol-gel transition – a crucial feature for materials that must flow during injection yet rapidly stabilize in situ. The fast self-healing and strong tissue adhesion properties stem from the strategic implementation of supramolecular assembly principles, likely involving a synergy of hydrogen bonding and electrostatic interactions. By achieving effective hemostasis and fluid sealing in vivo, this hydrogel system bridges the gap between synthetic versatility and biological functionality.

The challenge of regenerating hard tissues like bone exemplifies the need for hydrogels that balance mechanical robustness with bioactivity, a goal that builds directly on the network design strategies and processing techniques discussed earlier. Jiang et al.'s work[85] on regenerated silk fibroin/gelatin (RSF/G) hydrogels demonstrates how these principles can be synergistically combined to create materials tailored for load-bearing tissue reconstruction (Figure 10d). This approach leverages multiple cross–linking mechanisms to achieve superior mechanical properties. The combination of the physical and chemical cross–linking echoes the double network strategy, while the salt-assisted toughening through ammonium sulfate soaking capitalizes on the Hofmeister effect to enhance physical interactions between polymer chains. This multi-pronged strategy yields hydrogels with compressive and tensile moduli approaching those of native bone tissue, along with significant elongation capacity – a combination that addresses the longstanding challenge of creating hydrogels suitable for hard tissue applications. The observed promotion of osteogenic differentiation in vitro and enhanced bone regeneration in vivo underscore how carefully tuned mechanical properties can directly influence cellular behavior and tissue formation. This exemplifies the crucial interplay between material structure and biological function, a central theme in biopolymer-based hydrogel design. Moreover, the controlled degradation achieved in these hydrogels highlights the importance of temporal control in tissue engineering scaffolds. By matching the degradation rate to the pace of new tissue formation, these hydrogels create a dynamic environment that evolves with the regenerating tissue.

6.2. Bioindicators and Electronics

The molecular engineering principles and processing strategies explored earlier converge in the emerging field of bioelectronics and smart materials[86], where biopolymer-based hydrogels serve as a crucial bridge between biological and electronic systems. This intersection showcases how the unique properties of these materials can be harnessed to create multifunctional devices with unprecedented capabilities. Fu et al.'s self-healing structural color hydrogel[86c] exemplifies the synergistic combination of optical and dynamic properties achievable through strategic network design (**Figure 11a**). By integrating a GelMA inverse opal scaffold with an enzyme-containing BSA hydrogel,

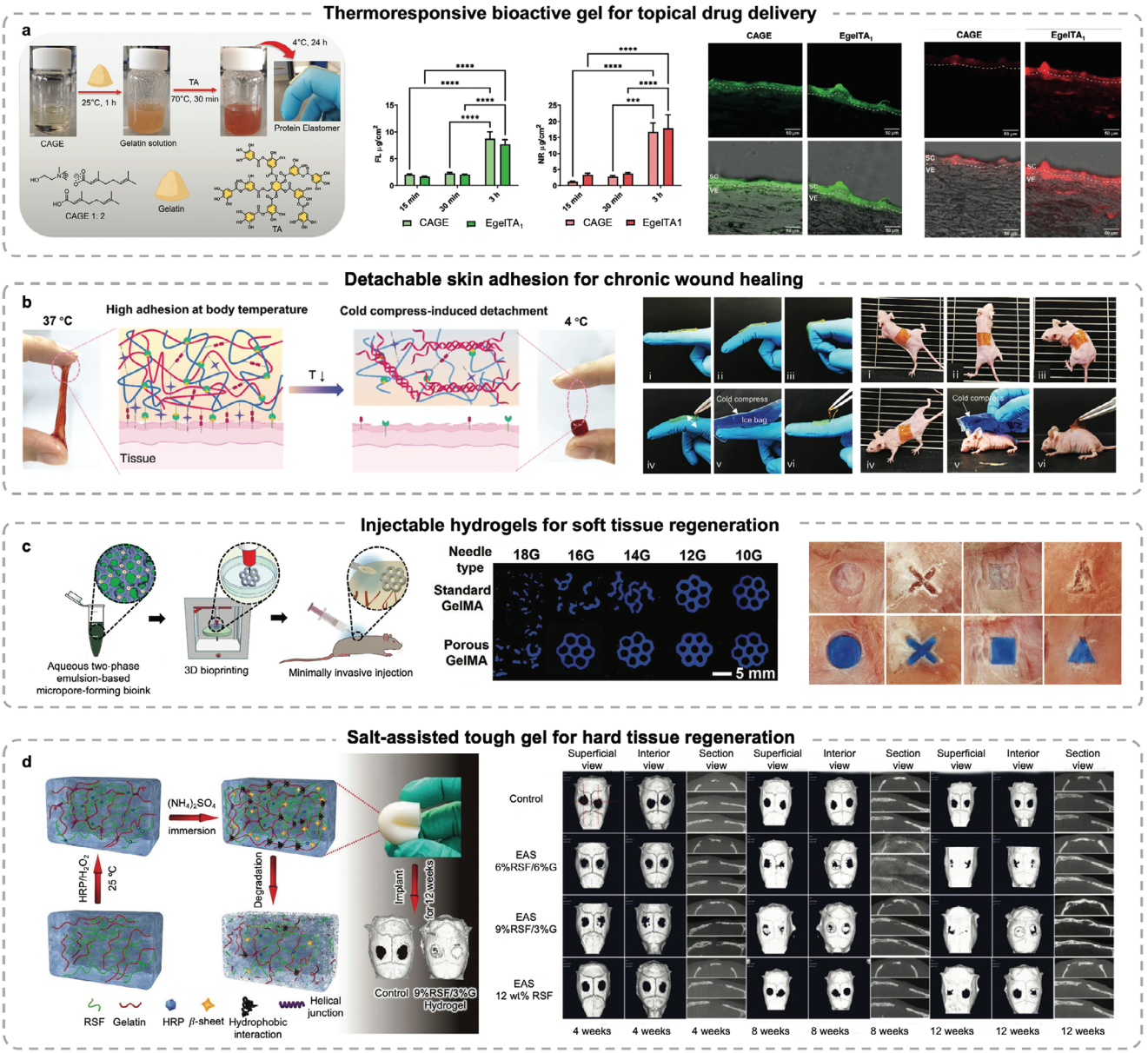

Figure 10. Biomedical applications of biopolymer-based hydrogels. a) Thermoresponsive bioactive gel for topical drug delivery, showing temperature-dependent gelation and drug release profiles. Adapted with permission.[82] Copyright 2024 Wiley-VCH. b) Detachable skin adhesion hydrogel for chronic wound healing, demonstrating strong adhesion at body temperature and cold-induced detachment. Adapted with permission.[83] Copyright 2023 Wiley-VCH. c) Injectable hydrogels for soft tissue regeneration, illustrating the fabrication process and shape retention capabilities. Adapted with permission.[84] Copyright 2021 Wiley-VCH. d) Salt-assisted tough gel for hard tissue regeneration, showing the toughening mechanism and improved bone regeneration in vivo. Adapted with permission.[85] Copyright 2019 Wiley-VCH.

this system leverages principles of supramolecular assembly and stimuli-responsive behavior. The result is a material that not only exhibits structural color but also possesses self-healing capabilities, demonstrating how careful molecular design can yield emergent properties at the macroscale. This approach opens new avenues for creating dynamic optical materials with potential applications ranging from anti-counterfeiting measures to adaptive biomedical devices.

In wearable technology, Yi et al.'s photonic skin[87] based on hydroxypropyl cellulose (HPC) illustrates how the inherent properties of biopolymers can be exploited to create sophisticated sensing platforms (Figure 11b). The combination of liquid crystalline and amorphous HPC layers in this device capitalizes on the material's unique phase behavior and responsive nature. This work demonstrates how molecular-level understanding of biopolymer structure and dynamics can be translated into macroscale devices with complex functionalities. The ability to create large-area, multipixel sensors that conform to irregular surfaces represents a significant advancement in biomimetic device design, bridging the gap between biological tissues and electronic systems.

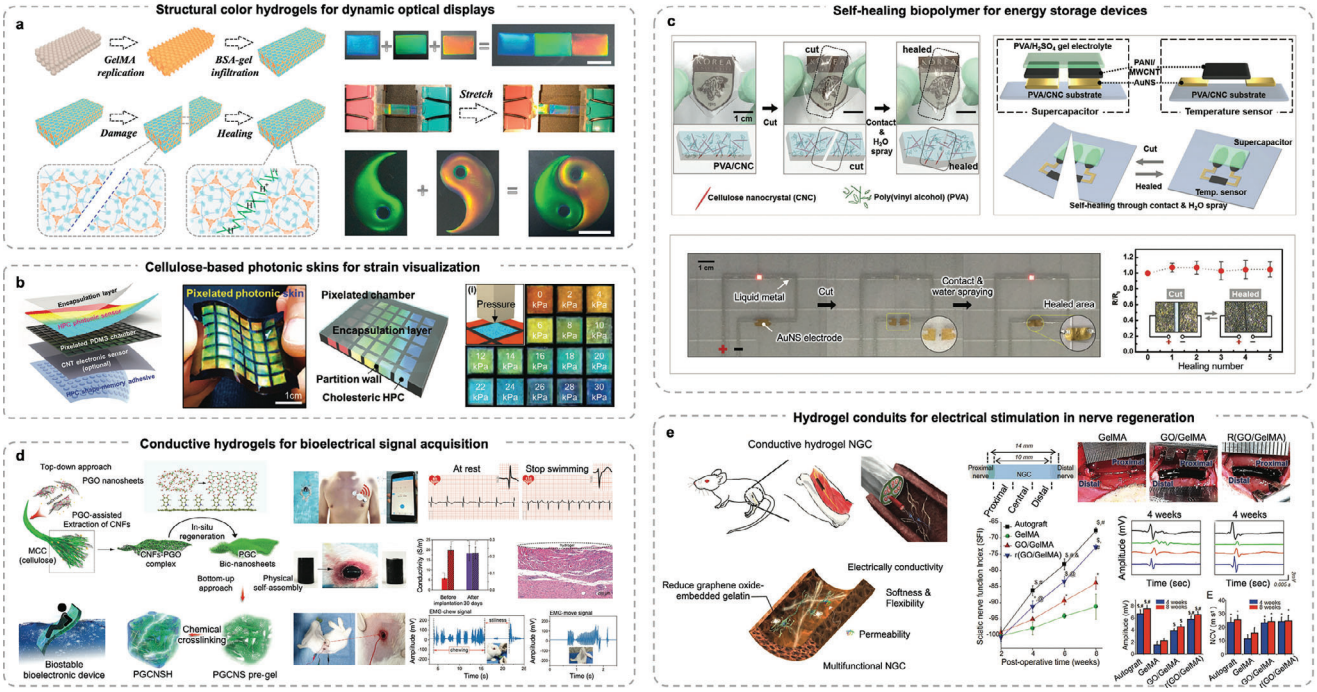

Figure 11. Functional materials and devices based on biopolymer-based hydrogels. a) Structural color hydrogels for dynamic optical displays are demonstrated, wherein color-changing and self-healing properties are exhibited. Adapted with permission.[86c] Copyright 2017 National Academy Of Sciences. b) Cellulose-based photonic skins for strain visualization are presented, with the multilayer structure and pressure-responsive color change being shown. Adapted with permission.[87] Copyright 2019 Wiley-VCH. c) Self-healing biopolymers for energy storage devices are illustrated, highlighting the healing process and maintained performance after damage. Adapted with permission.[88] Copyright 2019 Wiley-VCH. d) Conductive hydrogels for bioelectrical signal acquisition are displayed, with the fabrication process and application in ECG monitoring being demonstrated. Adapted with permission.[89] Copyright 2021 Wiley-VCH. e) Hydrogel conduits for electrical stimulation in nerve regeneration are showcased, wherein improved nerve recovery compared to traditional approaches is evidenced. Adapted with permission.[90] Copyright 2020 Wiley-VCH.

The development of conductive biopolymer-based hydrogels represents a significant leap in bridging the gap between biological tissues and electronic systems, building upon the molecular design principles and processing strategies discussed earlier. These materials exemplify how strategic combinations of biopolymers and conductive elements can yield multifunctional composites with unprecedented capabilities in bioelectronics. Kim et al.'s work[88] on PVA/CNC composite films showcases the synergy between polymer network design and nanocomposite reinforcement strategies (Figure 11c). By incorporating cellulose nanocrystals into a PVA matrix, they achieve a balance of flexibility, conductivity, and self-healing properties. This approach leverages the hydrogen bonding capabilities of both components to create a dynamic network capable of reforming after damage. The integration of functional electronic elements within this self-healing substrate demonstrates how molecular-level design can translate into macroscale device functionality, opening new avenues for resilient, wearable electronics. Yan et al.'s conductive cellulose bio-nanosheets[89] further illustrate the potential of biopolymer-based materials in creating stable, biocompatible electronic interfaces (Figure 11d). Their use of polydopamine-reduced graphene oxide as a template for cellulose assembly represents an innovative approach to controlling material structure at the nanoscale. This strategy results in a hydrogel with remarkable stability in physiological conditions, addressing a key challenge in developing long-term implantable electronics. The material's ability to support cell growth while maintaining electrical functionality showcases the unique advantage of biopolymer-based systems in creating truly biointegrated electronic devices.

The molecular engineering principles and processing strategies discussed earlier converge in cutting-edge applications of biopolymer-based hydrogels, particularly in neural tissue engineering and energy storage. These advancements demonstrate how tailored material properties can address complex challenges at the interface of biology and technology. Park et al.'s development of conductive hydrogel[90] nerve guidance conduits (NGCs) exemplifies the synergistic combination of biocompatibility and electrical functionality (Figure 11e). By incorporating reduced graphene oxide (rGO) into a GelMA matrix, they created a material that bridges the gap between soft tissues and electronic systems. This approach leverages the network design strategies and nanocomposite reinforcement techniques explored earlier to achieve a balance of mechanical flexibility, electrical conductivity, and biocompatibility. The significant improvements in nerve regeneration observed in vivo underscore how precisely engineered hydrogel properties can directly influence biological outcomes, showcasing the potential of these materials in creating functional neural interfaces.

Das et al.'s work[91a] on self-healing, ion-conducting hydrogels for energy storage devices represents another frontier in biopolymer applications. Their use of a poly(4-styrene sulfonate-co-methyl-uracil-imidazolium) chloride (PSS-MUI) and gelatin

system, cross–linked with ferric ions, demonstrates how complex polymer architectures can yield multifunctional materials. This approach combines principles of supramolecular assembly, dynamic bonding, and ion-mediated cross–linking to create hydrogels with a unique combination of properties: high ionic conductivity, stretchability, self-healing, and strong adhesion. The stable performance of these hydrogels in supercapacitor configurations, even after multiple damage-heal cycles, illustrates how molecular-level design can translate into robust, macroscale device functionality.

These advanced applications highlight the versatility of biopolymer-based hydrogels in creating materials that can seamlessly integrate with biological systems while providing sophisticated technological functions. By carefully tuning material properties through molecular design and processing techniques, researchers are pushing the boundaries of what's possible in bioelectronics, neural interfaces, and energy storage. Additionally, the integration of advanced flexible manufacturing and hydrogel electronics continues to drive progress in personalized health monitoring. For instance, Vasconcelos et al.[91b] recently reported an EEG 'e-tattoo' technology that can be printed directly on the scalp, enabling high-fidelity EEG signal acquistion. As our understanding of structure-property relationships in these complex systems continues to evolve, we can anticipate even more innovative applications that blur the lines between biological and electronic systems, paving the way for next-generation biointegrated technologies.

6.3. Stimuli-Responsive Materials

Abundant supramolecular interactions in the biopolymer-based hydrogels lay the foundation for creating materials with dynamic, adaptive behaviors. This capability is crucial for developing artificially intelligent systems that can effectively interface with and respond to the complex, ever-changing biological environments encountered in biomedical applications and creating bio-mimic stimuli-responsive color-changing,[57] shape-morphing,[53a,92] stiffness-varying materials[93] for cutting-edge applications such as camouflage skins, artificial muscles, and soft robotics.[94] By incorporating stimuli-responsive elements and dynamic interactions at the molecular level, we can imbue hydrogels with the ability to sense and react to specific cues, mimicking the adaptive nature of living tissues.[95] One particularly innovative approach in this field is the development of mechano-responsive degradation systems. Hwang et al.[96] demonstrated this concept by embedding hybrid vesicles within a calcium-cross–linked alginate hydrogel (**Figure 12a**). These vesicles, composed of phospholipids and amphiphilic block copolymers, encapsulate a calcium chelator (EGTA). When subjected to compressive stress, the vesicles rupture, releasing EGTA and triggering localized hydrogel degradation through calcium sequestration. This system exemplifies how tailored molecular design can translate into macroscale functional responses. The stability of the vesicles within the hydrogel matrix (maintaining integrity for over a month) highlights the importance of careful interfacial engineering. The dramatic response to mechanical stimuli – 90% weight reduction under 55 kPa stress – showcases the potential for achieving significant material property changes through relatively subtle molecular triggers.

The ability to control hydrogel behavior through environmental stimuli such as pH and humidity represents a significant advance in creating adaptive biopolymer systems. These responsive mechanisms not only expand the functional capabilities of hydrogels but also provide insights into the intricate relationships between molecular structure, environmental interactions, and macroscopic material properties. pH-responsive hydrogel formation and adhesion, as demonstrated by Hong et al.[97] with their boronic acid-modified alginate (Alg-BA) system, showcases how subtle changes in environmental chemistry can trigger dramatic shifts in material properties (Figure 12b). The transition from a viscoelastic solution to a gel upon pH increase relies on the precise tuning of boronic acid interactions. This molecular-level response translates into macroscale functionality, enabling the assembly of diverse hydrogel types and achieving adhesive strengths of up to 50 kPa. The versatility of this pH-responsive system in assembling hydrogels of varying compositions (alginate, agarose, polyacrylamide, and chitosan) underscores the importance of designing responsive elements that can interface with a broad range of biopolymer structures. This adaptability is crucial for creating complex, multi-component hydrogel constructs that more closely mimic the heterogeneity of natural tissues. The stability of these assembled structures over two weeks under agitation conditions demonstrates how molecular-level interactions can be leveraged to create durable macroscale architectures.

Humidity-responsive hydrogels, exemplified by Chen et al.'s[98] cellulose-based actuators, also illustrate how environmental stimuli can be harnessed to create dynamic, multifunctional materials (Figure 12c). The programmable bending behavior in response to humidity gradients requires a delicate balance between the hydrophilic and hydrophobic components of the hydrogel network. This balance is achieved through the hierarchical structuring of cellulose, polyvinyl alcohol, and polystyrene sulfonate, stabilized by supramolecular interactions. The high toughness (4.7 MJ m^{-3}) of these hydrogels stems from the synergistic reinforcement of soft and rigid networks within the structure. This combination of responsiveness and mechanical robustness is essential for applications requiring repeated actuation cycles without material degradation. The rapid self-healing capabilities under high humidity conditions, enabled by the reorganization of hydrogen bonds, further enhance the material's durability and functionality.

The development of hydrogels capable of transducing mechanical stimuli into electrical signals represents a leap forward in the integration of biopolymer materials with electronic systems. This capability is particularly crucial for the advancement of bioelectronics, where seamless interactions between biological tissues and electronic components are essential. The work by Yoon et al.[99] on ion-doped gelatin hydrogels (IGH) exemplifies how careful molecular engineering can endow hydrogels with sophisticated sensing capabilities (Figure 12d). The IGH system's ability to differentiate between contact and deformation through switchable ionic polarization highlights the importance of multimodal sensing in biomimetic materials. This functionality requires precise control over the hydrogel's structure and composition at multiple scales: i) Molecular level: The incorporation

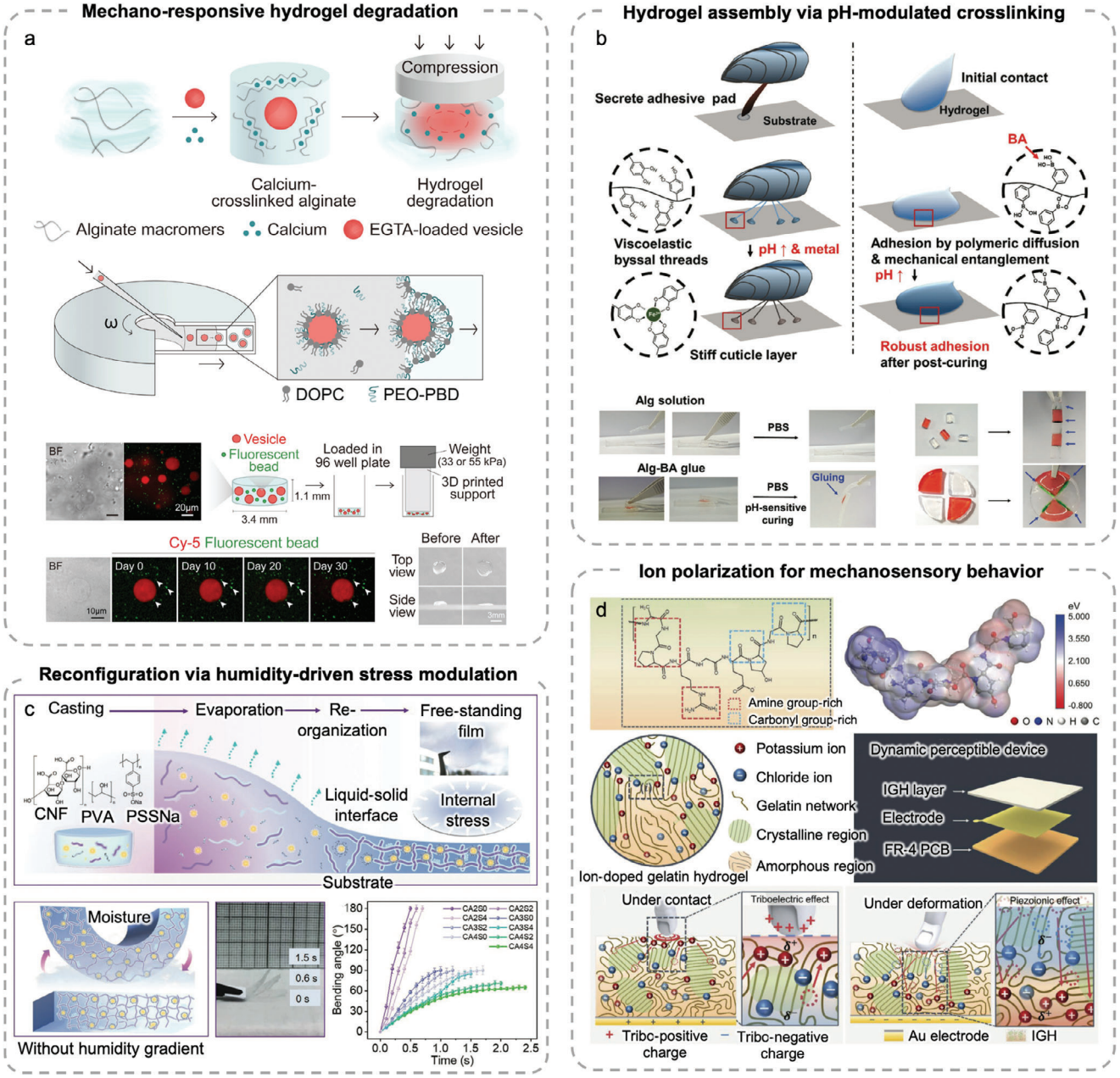

Figure 12. Dynamic responsiveness and stimuli-triggered functionalities in biopolymer-based hydrogels. a) Mechano-responsive hydrogel degradation: Schematic of calcium-cross–linked alginate hydrogel with embedded EGTA-loaded vesicles, hybrid vesicle composition, and fluorescence microscopy showing hydrogel degradation upon compression. Adapted with permission.[96] Copyright 2023 Wiley-VCH. b) Hydrogel assembly via pH-modulated cross–linking: Mechanism of pH-triggered adhesion using boronic acid-modified alginate and demonstration of pH-sensitive gelation and adhesion. Adapted with permission.[97] Copyright 2019 Wiley-VCH. c) Reconfiguration via humidity-driven stress modulation: Fabrication process of humidity-responsive cellulose-based actuators, bending behavior under humidity gradient, and stress–strain curves at different humidity levels. Adapted with permission.[98] Copyright 2022 Wiley-VCH. d) Ion polarization for mechanosensory behavior: Chemical structure and electrostatic potential map of gelatin, the schematic of ion-doped hydrogel sensor structure, and mechanisms of triboelectric and piezoionic sensing under contact and deformation. Adapted with permission.[99] Copyright 2021 Wiley-VCH.

and distribution of ions within the gelatin network must be optimized to enable both triboelectric and piezoionic effects. ii) Microstructure: The hydrogel's porous structure must facilitate ion mobility while maintaining mechanical integrity. iii) Macroscale: The overall hydrogel geometry must be designed to effectively transduce various mechanical inputs into distinct electrical outputs. The observed trade-off between deformation sensing and contact sensing sensitivity with changing ion concentration underscores the delicate balance required in material design. This relationship illustrates how molecular-level modifications (ion doping) directly influence macroscale functionalities (sensing performance).

7. Emerging Trends and Future Directions

As biopolymer-based hydrogel research advances, several promising directions are emerging that could significantly shape the future of this dynamic field. These directions build upon current progress while pushing the boundaries of what's possible with these versatile materials.

A key area of development is the creation of programmable, self-evolving hydrogels.[100] While current research has made strides in self-healing and stimuli-responsive materials, the next frontier involves hydrogels that actively evolve their structure and properties over time in predetermined ways.[101] These systems could gradually alter their mechanical properties to match the developmental stages of growing tissues, autonomously adjust degradation rates based on wound healing progress, or sequentially release multiple therapeutic agents without external intervention. Achieving this level of sophisticated behavior will require integrating time-dependent molecular switches or cascading reaction networks within the hydrogel structure, potentially drawing inspiration from synthetic biology.[102]

The concept of symbiotic living-synthetic hydrogel systems represents an exciting frontier.[103] Building on current work in cell-laden hydrogels, researchers could develop materials that form a true symbiosis with living cells or microorganisms.[104] In these dynamic, interactive environments, encapsulated cells might actively remodel and maintain the hydrogel matrix, while cellular metabolic products trigger specific hydrogel responses. Such systems could perform complex functions like sensing and responding to environmental toxins or producing therapeutic compounds on demand. Achieving this level of bio-integration will require a deep understanding of cell-material interactions and sophisticated interfaces between hydrogels and cellular machinery.

Advances in artificial intelligence and automated synthesis may lead to AI-designed and autonomously synthesized hydrogels.[105] This could involve AI algorithms predicting optimal hydrogel compositions, automated platforms rapidly fabricating and testing designs, and self-optimizing synthesis systems adjusting conditions in real time. Such approaches could accelerate material development and enable the creation of highly complex hydrogel systems that might be difficult for human researchers to conceptualize.[106]

Finally, incorporating principles from active matter physics could yield biopolymer-based hydrogels that function as dynamic, energy-consuming systems displaying complex collective behaviors. These materials might utilize biological processes to maintain non-equilibrium states, exhibit collective motion or shape changes in response to subtle cues, or self-assemble into complex structures.[107] Developing such systems will require integrating concepts from soft matter physics, non-equilibrium thermodynamics, and biology with hydrogel material science.

8. Conclusions

This review has traced the evolution of biopolymer-based hydrogels from fundamental molecular design principles to cutting-edge applications, revealing the profound impact of interdisciplinary approaches in materials science. By examining the interplay between network architecture, processing strategies, and resulting material properties, we have illuminated the complex structure-function relationships that govern hydrogel behavior across multiple scales. Our analysis highlights how strategic combinations of molecular engineering techniques and advanced fabrication methods have dramatically expanded the functional repertoire of biopolymer-based hydrogels. The ability to precisely control material properties—from nanoscale molecular interactions to macroscale structures—has enabled the creation of hydrogels that not only mimic but also enhance natural biological processes. This level of control represents a significant leap forward in our capacity to design materials that can dynamically interact with and respond to complex biological environments.

The diverse applications of biopolymer-based hydrogels discussed in this review underscore their versatility and potential to address critical challenges in healthcare and technology. From smart drug delivery systems and adaptive wound dressings to tissue engineering scaffolds and bioelectronic interfaces, these materials are bridging the gap between synthetic technologies and living systems. The emergence of hydrogels capable of evolving in response to biological cues or integrating seamlessly with electronic components points toward a future where the boundaries between natural and artificial systems become increasingly blurred. As we continue to unravel the intricate relationships between molecular structure, material properties, and biological function, biopolymer-based hydrogels are poised to play a pivotal role in addressing some of the most pressing challenges of our time. From advancing sustainable technologies to enabling new paradigms in medicine, these materials exemplify the power of interdisciplinary science to drive innovation. The ongoing evolution of biopolymer-based hydrogels not only pushes the boundaries of materials science but also offers a glimpse into a future where synthetic materials can seamlessly interface with, support, and enhance biological systems.

Acknowledgements

This work is supported by grants from the Johnson & Johnson WISTEM2D Scholar award, the American Chemical Society (GR-63402), the Office of Naval Research (ONR) awards (N000142412187 and N000142212595), and the Moore Foundation Award (12072).

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

C.W.Z. and M.S. contributed equally to this work. C.W.Z., M.S., and X.H. wrote and revised the manuscript, and X.H. supervised this study. The manuscript was written through the contributions of all authors, and all authors have approved the final version of the manuscript.

Keywords

biopolymer-based hydrogels, biomedical applications, hierarchical structuring, molecular engineering, structure-property relationships

Received: September 30, 2024
Revised: February 13, 2025
Published online:

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