Advances in Dual-Crosslinking Strategies for Hydrogels: From Physical-Chemical Synergy to Stimuli-Responsive Control

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Abstract. Population aging and the rising burden of trauma and chronic disease have increased the demands placed on biomedical hydrogels. In addition to biocompatibility, these materials are expected to provide mechanical support, processability, and environmental responsiveness. A single crosslinked network rarely balances all of these requirements. Dual-crosslinked networks, which combine reversible physical interactions with stable chemical bonds, have therefore received increasing attention. This review examines the network-forming mechanisms of dual-crosslinked hydrogels, with emphasis on how crosslinking density, degree of oxidation, and energy-dissipation structures affect mechanical behavior. Strategies for pH-, temperature-, light-, and redox-responsive functions and the corresponding characterization methods are also summarized. Available studies indicate that a suitable combination of two crosslinking mechanisms can improve strength, toughness, and tissue adhesion while retaining injectability, self-healing, and stimulus responsiveness to varying degrees. We further discuss translational barriers, including degradation-rate matching, coupling among performance parameters, and scale-up. This review is intended to support the structural design of hydrogels for tissue regeneration, drug delivery, and flexible bioelectronics.

Keywords: dual-crosslinked hydrogels, physical-chemical synergy, stimuli-responsive behavior, mechanical regulation, biomedical applications.

1. Introduction

Hydrogels have a high water content, generally good biocompatibility, and tunable network structures, which makes them widely useful in tissue engineering and drug delivery. Their three-dimensional hydrated networks can partly reproduce features of the extracellular matrix (ECM) microenvironment, as illustrated by 3D-printed nanocellulose-based hydrogels for biomedical processing [1]. A single crosslinking mode, however, usually favors only part of the required performance. Physical networks are maintained by relatively weak interactions and can be disturbed by ionic strength, temperature, and other environmental factors, which may limit load-bearing capacity and long-term stability [2]. Permanent covalent networks are more stable, but restricted chain mobility can make them brittle and can reduce their ability to combine injectability, self-healing, and stimulus responsiveness [3,4]. For the chitosan system, introducing a second crosslinking pathway increased the Young's modulus from 9.2 ± 1.0 kPa to 26 ± 2.8 kPa [5]. This result shows that network architecture can directly alter the mechanical microenvironment sensed by cells.

These trade-offs have driven the development of dual-crosslinking strategies. The underlying idea is not simply to add more crosslinking points, but to use differences in bond lifetime and load-bearing behavior. A stable network preserves the overall shape, whereas reversible interactions contribute to stress relaxation, shear thinning, or network reconstruction after damage. In a poly(aspartic acid)-PEG system, for example, a preformed hydrogen-bonded network supports flow and recovery during injection, and Ca^{2+} coordination subsequently reinforces the material in a Ca^{2+}-rich environment, which is useful for filling irregular bone defects [6]. An ECM-mimetic hydrogel combining dynamic covalent bonds with photopolymerization can tolerate 90% compressive strain and shows pH-dependent behavior, supporting cell delivery and three-dimensional culture [7]. Related materials have been investigated for vascular embolization [8], corneal repair [9], diabetic and infected wound treatment [10,11,12], neural injury repair [13], and cartilage regeneration [14]. Radiopaque or conductive components can further extend these systems to X-ray tracking and real-time sensing

[15,16]. Such studies provide a materials basis for applications including precision drug delivery, although clinical value will still depend on long-term safety and manufacturing consistency [4,17,18].

In terms of performance origin, physical crosslinking mainly contributes reversibility and processing adaptability, whereas chemical crosslinking mainly supports network retention and resistance to swelling. Each approach has clear advantages as well as limitations. Dual-crosslinked hydrogels should therefore be evaluated by considering strength, toughness, relaxation behavior, processability, and biological effects together, rather than judging performance only from modulus. Table 1 summarizes the main features and representative uses of single physical, single chemical, and dual-crosslinked networks.

This review first compares the roles of different crosslinking modes and then discusses mechanical regulation and stimuli-responsive functions in representative matrices, including chitosan, alginate, hyaluronic acid, and cellulose. The final section considers whether in vivo degradation can match the tissue-repair period, whether high strength can be combined with rapid response, and how complex preparation procedures may be standardized for scale-up.

Table 1. Comparison of the properties and applications of hydrogels with different crosslinking modes

Crosslinking type	Main interactions	Mechanical characteristics	Dynamics and processing	Biological features	Main limitations	Representative uses
Single physical [2]	Hydrogen bonding, electrostatic interactions, hydrophobic association, or coordination	Generally soft; strength and long-term stability depend on network type	Highly reversible; often shear-thinning, self-healing, or injectable	Stimulus responsiveness can be introduced readily; usually no residue from permanent crosslinkers	Sensitive to temperature, pH, and ionic environment	Short-term delivery; injectable carriers
Single chemical [3,4]	Permanent or dynamic covalent crosslinking	Good shape retention and swelling resistance; permanent networks may be brittle	Permanent networks are difficult to reshape after formation; dynamic covalent systems retain some reversibility	High stability, but initiators, crosslinkers, and residual groups require evaluation	Stress concentration may occur; responsiveness depends on bond type	Long-term scaffolds; coatings; in situ gelation
Dual crosslinking [6,14]	Two independent crosslinking pathways, including physical-chemical, dual-physical, or dual-chemical combinations	May improve strength, toughness, and fatigue resistance; the magnitude depends on the system	Tunable balance among stability, injectability, and recovery	Facilitates integration of adhesion, release, and sensing functions	More complex formulations and gelation procedures; strong coupling among parameters	Tissue repair; wound dressings; sensing devices

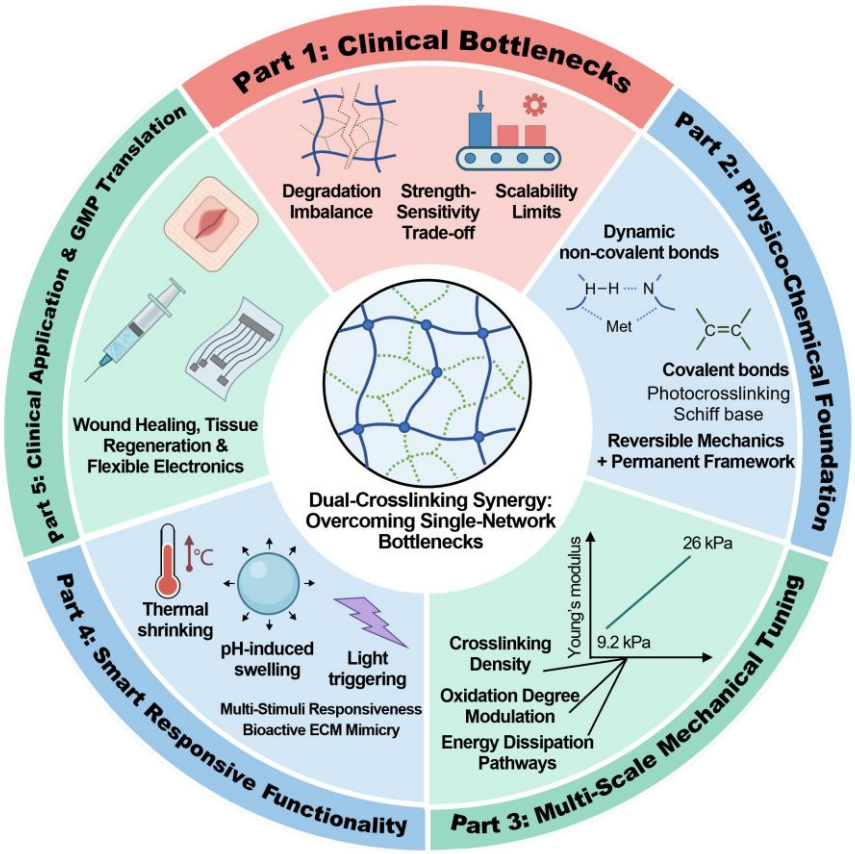

Figure 1. Technical roadmap of this review on dual-crosslinked hydrogels

2. Physicochemical Basis of Dual-Crosslinked Hydrogel Systems

2.1. Physical Crosslinking Mechanisms

Physical crosslinking organizes polymer chains into reversible networks through noncovalent interactions, most commonly hydrogen bonding, electrostatic attraction, hydrophobic association, and metal-ion coordination. Because these interactions have relatively low binding energies, they can break and reform under mechanical loading or environmental changes, which favors shear thinning, self-healing, and dynamic response. The properties of a specific system depend on how these interactions work together. In sodium alginate composite hydrogels, nanoparticles and Ca^{2+} coordination jointly improve mechanical strength and antifouling behavior [19]. Poly(aspartic acid)-based block copolymers first form a multiple hydrogen-bond network with tannic acid and are further tightened by local Ca^{2+} after injection, showing potential for bone repair [6]. An electrostatically crosslinked hyaluronic acid/ε-polylysine network can be adjusted to a hardness of 10-30 kPa and, under the reported experimental conditions, remained stable for more than 28 d while achieving 99.999% antibacterial activity [20]. In chitosan hydrogel fibers, hydrogen bonding combined with Al^{3+} coordination enabled the material to sustain a stress of 656 kPa and an elongation above 300% [15]. These findings show that a physical network is not necessarily weak; its mechanical limit depends on the density of interaction sites, the degree of cooperativity, and the network topology.

2.2. Chemical Crosslinking Mechanisms

Chemical crosslinking fixes network junctions through covalent bonds and usually reduces swelling, improves dimensional stability, and increases long-term load-bearing capacity. Common routes include free-radical polymerization, Schiff-base reactions, click chemistry, and light-induced crosslinking. Dynamic covalent bonds such as Schiff-base linkages combine covalent stability with a certain degree of reversibility. MBAA-mediated free-radical polymerization can create permanent

junctions between chitosan chains, which then work with noncovalent interactions to form a composite network [15]. In a soybean-protein system, Schiff-base bonds and metal-phenolic coordination form a double dynamic network with a storage modulus of 26.86 kPa, while drug release changes with pH [21]. Photocrosslinking offers control over where and when gelation occurs and is suitable for corneal adhesion and bio-3D printing [9,22]. Click reactions combined with light exposure can also be used to construct networks with shape-memory behavior or relatively high compressive modulus [10,13]. The biological effect of chemical crosslinking is not necessarily unidirectional. In the hyaluronic acid/ε-polylysine system, the chemically crosslinked sample showed weaker antibacterial activity than the purely physical network but better cell viability [20]. The extent of chemical crosslinking should therefore be selected according to the target tissue and intended service period rather than maximized without considering other requirements.

2.3. Synergistic Effects of Physical-Chemical Crosslinking

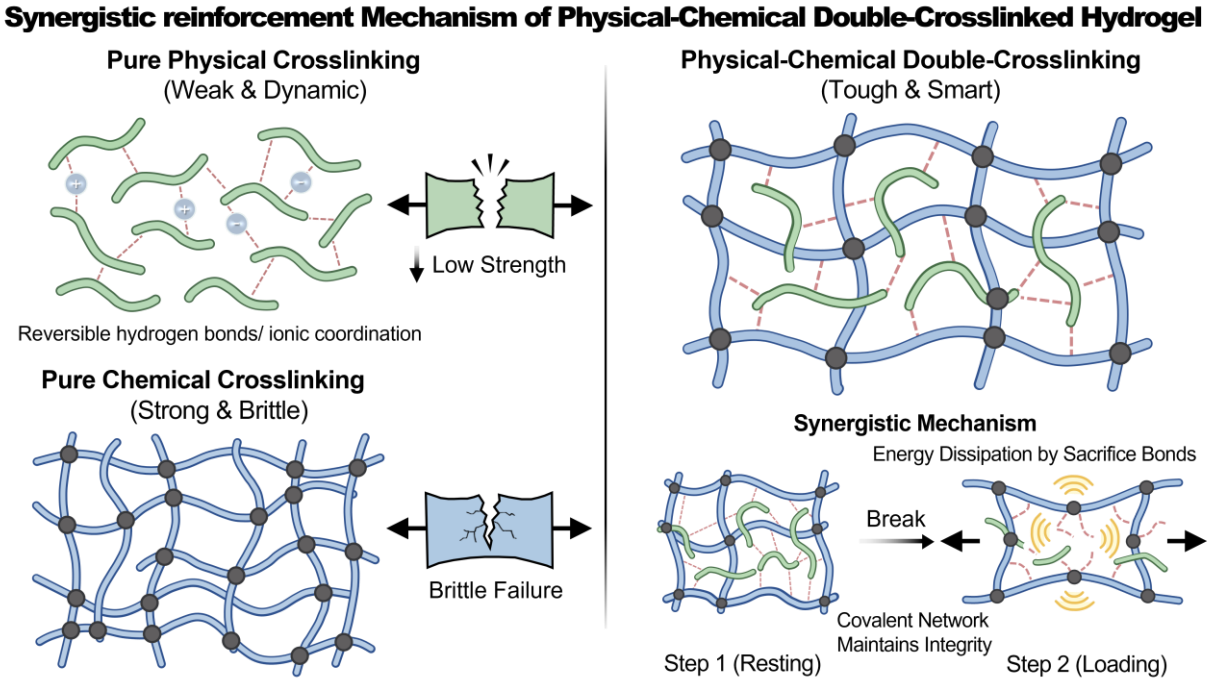

Figure 2. Schematic illustration of the synergistic reinforcement mechanism in physical-chemical dual-crosslinked hydrogels

The synergistic reinforcement shown in Figure 2 can be understood in terms of a load-bearing network and an energy-dissipating network. The covalent network maintains geometric integrity over longer time scales, while reversible hydrogen bonds, coordination bonds, and similar interactions preferentially dissociate during loading, redistribute stress, and partly reform after unloading. Chitosan-gallic acid modified hydrogels combine chain entanglement with chemical self-crosslinking to improve tissue adhesion and hemostatic performance [23]. Chitosan/Al^{3+} composite hydrogel fibers dissipate energy through the dissociation and re-formation of coordination junctions during stretching [15]. Dual crosslinking is a broader concept than physical-chemical crosslinking and also includes dual-physical and dual-chemical networks. In anthracene-functionalized chitosan, both anthracene photodimerization and free-radical photopolymerization of methacrylated chitosan are covalent processes. The Young's modulus increased from 9.2±1.0 kPa in the single-crosslinked material to 26±2.8 kPa after the second covalent pathway was added [5]. This example shows that independent crosslinking routes can effectively tune stiffness, but this particular system should not be classified directly as a physical-chemical synergistic network. Additional structural features, such as microphase separation, bicontinuous networks, and hierarchical architectures, can alter crack propagation, damping, and tensile behavior, thereby translating molecular-scale bond exchange into macroscopic energy dissipation [24,25].

3. Mechanical Regulation of Dual-Crosslinked Systems

3.1. Relationship Between Crosslinking Density and Mechanical Strength

In a dual-crosslinked network, crosslinking density determines the effective chain length and the available space for molecular motion, making it an important factor in both modulus and failure mode. Within a range where the network is not overconstrained, increasing the number of effective crosslinks generally raises the storage modulus and tensile or compressive strength. Beyond an appropriate range, however, restricted chain extension and stronger stress concentration may reduce toughness. By adjusting the crosslinking sequence and component ratio, a porous SA/Gel/PVA composite hydrogel achieved an increase of more than 20% in overall mechanical strength [26]. A cellulose system containing the HECM macromolecular monomer formed a double network and showed a self-strengthening efficiency of 124.7% during cyclic compression, indicating contributions from network rearrangement and energy-dissipating structures [27]. In GP/Zn-VHC nanocomposite hydrogels, a photo-initiated covalent network together with Zn^{2+} coordination improved fracture stress and toughness [28]. In contrast, an excessive proportion of quaternized chitosan enlarged the pore structure in a chitosan/quaternized-chitosan system but weakened its overall mechanical properties [29]. Optimization of crosslinking density should therefore account for matrix-chain rigidity, functional-group content, water content, and the intended load.

3.2. Effect of Oxidation Degree on Viscoelasticity

For aldehyde-containing polysaccharide systems, the degree of oxidation first changes the number of reactive sites and then affects the formation rate of dynamic covalent bonds, network relaxation, and viscoelasticity. In AOP127/ODex hydrogels, dynamic oxime bonds provide a printable first network at low temperature. As the temperature rises, hydrophobic association of PPO segments forms a second network, increasing both toughness and thermal responsiveness [30]. In oxidized pectin coatings, the oxidation level influences the stability of the subsequent EDC/NHS-crosslinked network. A heparin-loaded coating prepared by this route showed mechanical properties comparable to those of a glutaraldehyde-crosslinked system, together with favorable hemocompatibility and anticalcification behavior [31]. In hyaluronic acid hydrogels, changing the molar ratio of hydrazide to aldehyde groups alters swelling, microstructure, and mechanical properties while retaining pH responsiveness and cell affinity [32]. The role of oxidation therefore cannot be reduced to a simple increase in the number of crosslinks. Too little oxidation may produce an incomplete network, while excessive oxidation may over-restrict chain motion or accelerate damage to the polysaccharide backbone. Practical design requires a balance among reactivity, relaxation time, and biocompatibility.

3.3. Strategies for Optimizing Dynamic Mechanical Properties

The aim of dynamic mechanical optimization is to maintain hydrogel function during repeated deformation and in complex physiological media, rather than merely to obtain a high initial strength. Current approaches mainly include introducing exchangeable bonds, incorporating sacrificial energy-dissipating units, and building hierarchical networks. A CMC-PAM-LM hydrogel combining Ga^{3+} coordination with covalent polymerization reached a fracture strain of 778.24% and a fracture stress of 114.81 kPa. It remained functional after more than 800 fatigue cycles and showed a strain-response time of about 30 ms [16]. The sequentially crosslinked Gel/Alg-CDH-Ca-EDC system had a tensile strength of 1.068 MPa and a toughness of 677.6 kJ/m^3, with a mechanical range close to that of native corneal tissue [33]. In another hierarchical reinforcement strategy, dynamic hydrazone bonds, double-bond crosslinking, and thermoresponsive shape-memory short fibers increased stiffness from 9.27 kPa to 53.40 kPa while preserving injectability [34]. Modified bovine serum albumin can form spring-like secondary structures that act as energy-dissipating units and improve tensile and interfacial adhesion properties [35]. These examples indicate that bond type is only one design variable; spatial distribution, exchange rate, and the ratio of dynamic to permanent junctions are also central to fatigue life and recovery efficiency.

4. Functionalization and Characterization of Smart Dual-Crosslinked Hydrogel Systems

4.1. Stimuli-Responsive Behavior and Dynamic Properties

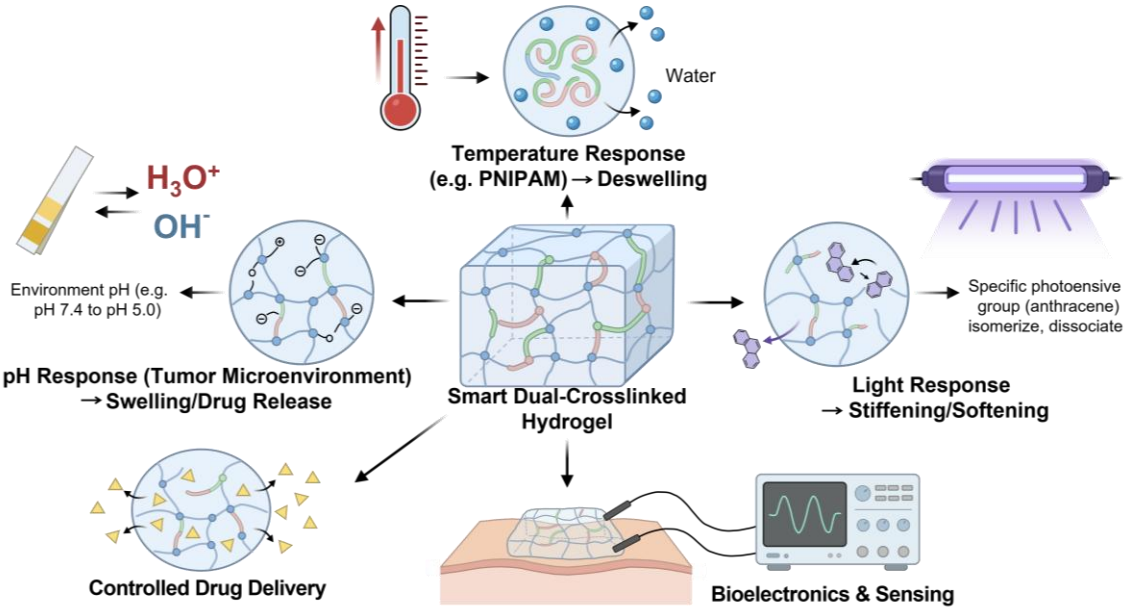

Figure 3. Schematic illustration of functional integration in multi-stimuli-responsive dual-crosslinked smart hydrogels

Figure 3 summarizes common stimulus-structure-function relationships in smart dual-crosslinked hydrogels. pH response usually arises from protonation/deprotonation of ionizable groups or shifts in dynamic-bond equilibria, leading to network swelling, contraction, or dissociation. Poly(acrylic acid) hydrogels can be used for pH monitoring in synovial fluid, while Schiff-base networks can exploit differences in the tumor microenvironment to regulate drug release [36,37]. Temperature response is often introduced through polymers such as PNIPAM, where a hydrophilic-to-hydrophobic transition causes chain contraction upon heating and can regulate molecular diffusion. HPC/LMA micellar hydrogels combine low-temperature antifreezing behavior with a rapid optical response [38,39], while ethanol content and salt concentration can further influence conductivity and light scattering [40]. A single stimulus may therefore change not only network volume but also transport, electrical, or optical signals, depending on how the crosslinked network is coupled to functional components.

Responsive behavior is limited not only by network dimensions and dynamic-bond exchange rates, but also by how efficiently a functional structure converts an environmental change into a measurable output. A lower effective crosslinking density and more flexible chains can facilitate conformational rearrangement, although they may also weaken shape retention. A bioinspired leaf-stomata structure can translate changes in humidity into opening and closing of pores in a fabric [41]. Rare-earth/polymer composite networks can produce multicolor fluorescence under biaxial stretching for motion monitoring and dynamic information encryption [42]. MXene-containing PNIPAM smart dressings integrate strain sensing with near-infrared-controlled release and can reach a strain-response time of about 160 ms [43]. In gelation and detection, carbon quantum dots can catalyze visible-light polymerization and complete network formation within 1 min [44], while an orange-emitting silicon-quantum-dot fiber sensor maintains stable pH detection over a broad range [45]. These examples represent different processes, including actuation, signal output, drug release, gelation, and detection, and should not be grouped under a single definition of response time.

Reversibility in dynamic networks can be provided by hydrogen bonds, metal coordination, boronate esters, Schiff-base bonds, or disulfide bonds, each with a different sensitivity to pH, glucose concentration, or redox conditions. Combining electrostatic interactions with hydrophobic association can support both wet adhesion and mechanical loading [46]. Boronate ester/Schiff-base

composite networks are well suited to the chemical microenvironment of diabetic wounds and can sustain the release of nanozymes or antibacterial particles [47]. In redox/light dual-responsive systems, disulfide bonds combined with photosensitive groups can enable light-triggered pulsatile release accompanied by adaptive changes in network stiffness [48]. Bisphosphonate-based hydrogels can regulate bone remodeling through a biomimetic negative-feedback effect on osteoclast activity [49]. Multi-responsive design should therefore focus not only on adding more types of stimuli, but also on the compatibility among response modules and their selectivity under physiological conditions.

4.2. Biocompatibility and Functional Design

Several studies have shown that dual-crosslinked networks based mainly on natural polymers can maintain good cell viability, although compatibility still depends on the degree of modification, residual reactants, and crosslinking conditions. Thiolated mussel-inspired chitosan [50], photocrosslinked chitosan [5], and chondroitin sulfate/gelatin systems [7] have all shown favorable cell survival. POSS-containing composite hydrogels can also promote osteogenic differentiation of stem cells, providing a route for functional bone repair [51]. A natural origin, however, does not replace systematic evaluation of cytotoxicity and in vivo safety. Mechanical enhancement and biological effects need to be considered together during material design.

Dual-crosslinked networks can also regulate drug release by changing mesh size, bond-exchange rate, and drug-matrix interactions. A soybean protein/oxidized dextran system uses Schiff-base bonds together with a gallic acid-Fe3+ metal-phenolic network to control curcumin release, with both swelling and release varying with pH [21]. HAMA hydrogels can provide co-delivery of ocular therapeutics for as long as 45 d [52]. Nanocellulose-reinforced collagen hydrogels have been used for sustained local anti-inflammatory delivery to the cornea [53], while dual-crosslinked gelatin/dextran medical hydrogels combine dynamic condensation with photopolymerization to balance gelation and structural retention [54]. Release performance is therefore not an isolated parameter, but an outcome of crosslinking density, degradation, drug-matrix interactions, and tissue loading.

To improve integration at the material-tissue interface, dual-crosslinked systems often borrow adhesive groups and fibrous structures from the ECM. Catechol-metal coordination can strengthen adhesion to wet tissues [50]. Nanofibrillar peptide hydrogels can release hemostatic, anti-inflammatory, or antibacterial components in response to the wound microenvironment [55]. Polysaccharide networks loaded with antibacterial carbon dots combine pH-dependent release with broad-spectrum antibacterial activity [56]. Microfluidic fabrication can also generate pH-sensitive alginate microgels with relatively uniform size and composition for intestinally targeted delivery [57]. The common goal of these biomimetic and processing strategies is to better match the spatial location, release schedule, and interfacial mechanics of the material to actual therapeutic needs.

4.3. Advanced Characterization and Research Methods

Crosslinking density is difficult to determine from a single experiment and is usually assessed by combining information on molecular mobility, rheology, and structural length scales. LF-NMR reflects water states and chain constraints; when combined with rheological testing and SAXS, it can help analyze polymer interactions and the distribution of network junctions [58,59]. In phototunable hybrid-hydrogel models, chemical modification of the matrix and photopolymerization conditions can be used to alter local stiffness [60]. In controllable transdermal hydrogel microneedles, polymer-homologue-mediated network formation affects molding stability and release behavior [61]. These studies indicate that modulus, swelling, and mesh size provide only indirect comparisons of network density. Crosslinking densities inferred from models should therefore be checked against chemical conversion and scattering measurements.

Dynamic mechanical characterization includes more than instantaneous modulus. Frequency dependence, stress relaxation, hysteretic loss, and cyclic damage are also important. Oscillatory rheology, DMA, and tensile/compressive fatigue testing can be used to characterize the linear viscoelastic region, temperature- and frequency-dependent behavior, and durability, respectively

[16,62,63]. Passive nanorheology obtains local viscoelastic information from the thermal motion of tracer particles and can capture microscale changes that may be difficult to resolve with bulk instruments [64]. For conductive hydrogels with many formulation variables, high-throughput experimental platforms can screen composition-property relationships in parallel and improve optimization efficiency [65]. Because these methods probe different time scales, the resulting data should be interpreted in relation to the actual loading conditions expected in use.

Imaging and scattering methods are used to examine network topology, phase domains, and pore structures. SAXS provides statistical information at the nanoscale, whereas SEM shows the morphology of the dried network skeleton [59]. For cell-laden materials, structural imaging and cell imaging should be interpreted together with mechanical data. Studies of oxidized-hyaluronic-acid hydrogels for neural tissue engineering, for example, need to consider matrix stiffness, microstructure, and primary-neuron responses at the same time [66]. CT and MRI can track the in vivo position and shape changes of hydrogels [67], but imaging signals generally cannot replace direct mechanical measurements. Establishing links among molecular interactions, microstructure, and macroscopic properties therefore requires combined use of in situ imaging, rheology, and mechanical testing. Table 2 summarizes the crosslinking mechanisms, key parameters, and application directions of several representative systems.

Table 2. Key properties and applications of representative dual-crosslinked hydrogel systems

Matrix material	Dual-crosslinking mechanism	Key mechanical parameters	Responsive/functional features	Main applications
Chitosan-anthracene/photopolymerization system [5]	Anthracene photodimerization (covalent) + free-radical photopolymerization of methacrylated chitosan (covalent)	Young's modulus 26±2.8 kPa (single-crosslinked control: 9.2±1.0 kPa)	Light-controlled stiffness; dual-covalent crosslinking reference system	Cell culture; tissue engineering
Soybean-protein dynamic crosslinking system [21]	Schiff-base bonds (dynamic covalent) + gallic acid-Fe^{3+} metal-phenolic coordination (noncovalent)	Storage modulus 26.86 kPa	pH-dependent swelling and release	Controlled curcumin delivery
Cellulose/liquid-metal composite system [16]	Ga^{3+} coordination (noncovalent) + covalent polymerization	Fracture strain 778.24%; fracture stress 114.81 kPa; withstands >800 fatigue cycles	Strain sensing and conductive response	Wearable sensing
Gelatin/sodium-alginate sequential crosslinking system [33]	Ca^{2+} ionic crosslinking (noncovalent) + EDC/NHS covalent crosslinking	Tensile strength 1.068 MPa; toughness 677.6 kJ/m³	Biodegradable; tunable structure	Corneal regeneration; tissue scaffolds
Hyaluronic acid/ε-polylysine system [20]	Electrostatic interactions (noncovalent) + covalent crosslinking	Hardness 10-30 kPa	pH-dependent behavior and antibacterial activity	Infected wound repair
Poly(aspartic acid)-PEG composite system [6]	Multiple hydrogen bonds + Ca^{2+} coordination (dual noncovalent crosslinking)	Injectable; enhanced stability in a Ca^{2+}-rich environment	Shear thinning, self-healing, and ion-triggered reinforcement	Bone-defect filling and repair

Table 2 shows that dual-crosslinking designs have been applied to a range of settings, including bone-defect repair, corneal regeneration, treatment of infected wounds, and wearable sensing. The performance priorities differ among these applications. Tissue scaffolds place greater emphasis on modulus, toughness, and degradation matching, whereas sensing materials also require stable conductivity, fatigue resistance, and rapid response. Although laboratory studies show clear potential, long-term in vivo behavior, trade-offs among properties, and batch-to-batch consistency remain common barriers. The following section discusses future priorities from the perspective of these translational issues.

5. Conclusions and Outlook

For dual-crosslinked hydrogels to move from laboratory studies toward clinical use, the first challenge is to match structural stability with the time scale of degradation. Networks that relax or degrade too quickly may lose mechanical support or drug-release function, whereas excessive crosslinking can hinder cell infiltration, tissue remodeling, and material clearance. A second challenge is the coupling among strength, toughness, and response rate. Increasing the fraction of permanent crosslinks often improves shape retention but may prolong relaxation and weaken self-healing. Third, some high-performance systems depend on multistep modification, photoinitiation, or metal coordination and have narrow reaction windows, which can lead to batch variation during scale-up. Evaluation for clinical translation should therefore move beyond isolated performance records and toward integrated validation of degradation, fatigue resistance, biosafety, and process reproducibility.

Future work should focus on quantifiable relationships among structure, properties, and function. At the molecular level, the exchange rates of different dynamic bonds and their stability in physiological media need to be established. At the network level, multiscale characterization should be used to connect crosslinking topology and energy dissipation with cell behavior. At the device and product level, sterilization, storage, processing windows, and batch consistency under GMP conditions must be considered. Dopamine/metal coordination, functional nanocomponents, and biomimetic fibrous structures may be used to build interfaces with wet adhesion, self-healing, and signal-output functions, but their long-term metabolism and safety limits still require systematic evaluation. Dual-crosslinked hydrogels are more likely to develop from passive carriers into platforms that actively regulate local microenvironments only when material performance is matched to disease conditions, tissue-repair time scales, and manufacturing requirements. Such systems may then support applications in tissue regeneration, precision drug delivery, and flexible bioelectronics.

References

[1] Jeon M J, Randhawa A, Kim H, et al. Electroconductive nanocellulose, a versatile hydrogel platform: From preparation to biomedical engineering applications[J]. Advanced Healthcare Materials, 2025, 14(3): 2403983.

[2] Wu X, Sun H, Qin Z, et al. Fully physically crosslinked pectin-based hydrogel with high stretchability and toughness for biomedical application[J]. International journal of biological macromolecules, 2020, 149: 707-716.

[3] Damm C, Goepferich A. Dual cross-linked hydrogels as promising materials for drug delivery[J]. International Journal of Pharmaceutics, 2025: 125929.

[4] Anwar M Z, Kathuria H, Er J X, et al. Hybrid hydrogels for biomedical applications: Addressing challenges in drug delivery through advanced crosslinking and nanocarrier integration[J]. Journal of Controlled Release, 2026: 114719.

[5] Batool S R, Nazeer M A, Yildiz E, et al. Chitosan-anthracene hydrogels as controlled stiffening networks[J]. International Journal of Biological Macromolecules, 2021, 185: 165-175.

[6] Chu W, Ke X, Dong Z, et al. Dual crosslinking hydrogels with tunable injectability and stability for bone repair[J]. Journal of Materials Chemistry B, 2022, 10(23): 4386-4394.

[7] Fu H, Yu C, Li X, et al. Facile engineering of ECM-mimetic injectable dual crosslinking hydrogels with excellent mechanical resilience, tissue adhesion, and biocompatibility[J]. Journal of Materials Chemistry B, 2021, 9(48): 10003-10014.

[8] Xie R, Chen Y C, Zhao Y, et al. Injectable hydrogel capable of in situ covalent crosslinking for permanent embolization[J]. ACS applied materials & interfaces, 2021, 13(48): 56988-56999.

[9] Nie X, Hui J, Han Z, et al. A natural corneal extracellular matrix-inspired dual-crosslinked hydrogel bioadhesive for emergency corneal trauma repair[J]. Acta Biomaterialia, 2026.

[10] Pu Y, Wang P, Yang R, et al. Bio-fabricated nanocomposite hydrogel with ROS scavenging and local oxygenation accelerates diabetic wound healing[J]. Journal of Materials Chemistry B, 2022, 10(21): 4083-4095.

[11] Cheng X, Wang Y, Qian J, et al. Injectable silk fibroin hydrogel encapsulating pH-Responsive ZnS nanoparticles for synergistic redox modulation and diabetic wound healing[J]. Biomaterials Advances, 2025: 214674.

[12] Huang Y, Kang H, Wang Y, et al. One stone three birds: silver sulfadiazine modulates the stability and dynamics of hydrogels for infected wound healing[J]. Advanced Healthcare Materials, 2024, 13(19): 2400242.

[13] Zhang D, Ren Y, He Y, et al. In situ forming and biocompatible hyaluronic acid hydrogel with reactive oxygen species-scavenging activity to improve traumatic brain injury repair by suppressing oxidative stress and neuroinflammation[J]. Materials Today Bio, 2022, 15: 100278.

[14] Chaudhary S, Jain S, Ghosal D, et al. Harnessing theraoenergetics for cartilage regeneration: Development of a therapeutic and bioenergetic loaded janus nanofiber reinforced hydrogel composite for cartilage regeneration[J]. ACS Biomaterials Science & Engineering, 2025, 11(5): 2792-2809.

[15] Nordin N, Azman Z A Z, Adnan N A, et al. On the dual crosslinking for functionality enhancement of poly (acrylamide-co-acrylic acid)/chitosan-aluminum (III) ions and its characterization and sensory hydrogel fibers[J]. International Journal of Biological Macromolecules, 2024, 274: 133383.

[16] Wang F, Wei Y, Bi M, et al. Dual-crosslinked liquid metal-cellulose hydrogels with synergistic conduction networks for multimodal wearable biosensing[J]. Biosensors and Bioelectronics, 2025, 288: 117801.

[17] Yan X, Huang H, Bakry A M, et al. Advances in enhancing the mechanical properties of biopolymer hydrogels via multi-strategic approaches[J]. International Journal of Biological Macromolecules, 2024, 272: 132583.

[18] Rodin M, Li J, Kuckling D. Dually cross-linked single networks: structures and applications[J]. Chemical Society Reviews, 2021, 50(14): 8147-8177.

[19] Dawit H, Mehmood S, Hussain Z, et al. Fabrication of nanoparticle-reinforced composite hydrogel for improved durability, antifouling, and thrombosis-resistance in arteriovenous grafts[J]. Colloids and Surfaces B: Biointerfaces, 2025, 247: 114420.

[20] Salma-Ancane K, Sceglovs A, Tracuma E, et al. Effect of crosslinking strategy on the biological, antibacterial and physicochemical performance of hyaluronic acid and ε-polylysine based hydrogels[J]. International journal of biological macromolecules, 2022, 208: 995-1008.

[21] Xu J, Yan S, Qi B, et al. New insights into the cross-linking mechanism of soybean protein-based double dynamic cross-linking hydrogels for the controlled delivery of curcumin[J]. Food Research International, 2025, 211: 116456.

[22] Yang X, Li X, Wu Z, et al. Photocrosslinked methacrylated natural macromolecular hydrogels for tissue engineering: A review[J]. International Journal of Biological Macromolecules, 2023, 246: 125570.

[23] Hwang S M, Kim E, Wu J, et al. Temperature-and pH-induced dual-crosslinked methylcellulose/chitosan-gallol conjugate composite hydrogels with improved mechanical, tissue adhesive, and hemostatic properties[J]. International Journal of Biological Macromolecules, 2024, 277: 134098.

[24] Zhang Y, Wang Q, Deng W, et al. “Grafting-to” Polymers of Xylan-g-allyl Glycidyl Ether Toughen PEG Hydrogel via Microphase Separation: Thermoresponsive and Photoreactive Molecular Assembly in DLP 3D Printing[J]. Small, 2025, 21(34): 2502129.

[25] Cai S, Chen W, Chen J, et al. Microphase-Separated Hydrogels With Low Hysteresis and High Damping for Flexible Protection and Electronics[J]. Small, 2025, 21(41): e07167.

[26] Zhang T, Liu H, Nie P, et al. Enhancement of alginate/gelatin/polyvinyl alcohol hydrogels for multi-crosslinked 3D printed blood vessels[J]. International Journal of Biological Macromolecules, 2025, 310: 142947.

[27] Sun W, Liu X, Hua W, et al. Self-strengthening and conductive cellulose composite hydrogel for high sensitivity strain sensor and flexible triboelectric nanogenerator[J]. International Journal of Biological Macromolecules, 2023, 248: 125900.

[28] Yue S, Wei Q, Wang L, et al. Halloysite and Zn2+-crosslinked gelatin/polyamidoxime-based hydrogel with immunoregulatory and antibacterial properties for promoting wound healing[J]. International Journal of Biological Macromolecules, 2026: 151229.

[29] Ding F, Hou H, Long S, et al. Electrodeposition of porous chitosan composite hydrogels with bromothymol blue for monitoring the spoilage of chicken breast[J]. International Journal of Biological Macromolecules, 2025: 149404.

[30] Li Z, Liu L, Chen Y. Direct 3D printing of thermosensitive AOP127-oxidized dextran hydrogel with dual dynamic crosslinking and high toughness[J]. Carbohydrate Polymers, 2022, 291: 119616.

[31] Hu M, Peng X, Yue L, et al. Well-designed two-fold crosslinked biological valve leaflets with heparin-loaded hydrogel coating for enhancing anticoagulation, endothelialization, and anticalcification[J]. Biomaterials Science, 2022, 10(19): 5535-5551.

[32] Zhang M, Chen X, Yang K, et al. Dual-crosslinked hyaluronic acid hydrogel with self-healing capacity and enhanced mechanical properties[J]. Carbohydrate Polymers, 2023, 301: 120372.

[33] Nie X, Tang Y, Wu T, et al. 3D printing sequentially strengthening high-strength natural polymer hydrogel bilayer scaffold for cornea regeneration. Regener Biomater 11: rbae012[EB/OL].(2024)

[34] Xu T, Che L, Du L, et al. Hierarchically Reinforcing Hydrogel for Multidimensional Bone Homeostasis Modulation to Regenerate Osteoporotic Defect[J]. Advanced Healthcare Materials, 2026, 15(1): e02337.

[35] Luo Y, Long K, Chen M, et al. Bovine Serum Albumin Crosslinked Hydrogels with Enhanced Mechanical Properties for Skin Bioelectronics[J]. Small, 2026, 22(29): e14711.

[36] Wijayaratna U N, Kiridena S D, Adams J D, et al. Synovial fluid pH sensor for early detection of prosthetic hip infections[J]. Advanced functional materials, 2021, 31(37): 2104124.

[37] Fan J, Cai X, Gui H, et al. Injectable polypeptide-polysaccharide depot for preventing postoperative tumor recurrence by concurrent in situ chemotherapy and brachytherapy[J]. Materials Today Bio, 2024, 28: 101219.

[38] Chen S, Yang Y, Niu L, et al. Microgel-crosslinked, thermo-and mechano-dual responsive, ketoprofen-loaded hydrogels with high mechanical properties and rapid response[J]. International Journal of Pharmaceutics, 2025: 126150.

[39] Zhang Z, Yao A, Cheng Z, et al. Thermoresponsive physically cross-linked hydrogels with bidirectional optical response for smart windows application[J]. ACS Applied Materials & Interfaces, 2025, 17(39): 54967.

[40] Xue Y, Lai X, Hong F, et al. Multistimuli-responsive conductive hydrogels for information encryption, decryption, and wearable sensors[J]. ACS Applied Materials & Interfaces, 2025, 17(43): 59832-59845.

[41] Yu Y, Chen Q, Ma B, et al. Bioinspired moisture-responsive smart knitted fabric with artificial leaf stomata based on polyacrylamide hydrogel[J]. ACS Applied Materials & Interfaces, 2025, 17(26): 38398-38410.

[42] Liu M, Hao Z, Li Y, et al. Biaxially stretchable rare earth–polymer multicolor fluorescent hydrogel for human motion monitoring and dynamic information encryption[J]. Small, 2025, 21(49): e09323.

[43] Hao F, Wang L, Chen B, et al. Bifunctional smart hydrogel dressing with strain sensitivity and NIR-responsive performance[J]. ACS applied materials & interfaces, 2021, 13(39): 46938-46950.

[44] Qiao L, Zhou M, Shi G, et al. Ultrafast visible-light-induced ATRP in aqueous media with carbon quantum dots as the catalyst and its application for 3D printing[J]. Journal of the American Chemical Society, 2022, 144(22): 9817-9826.

[45] Li D, Li X, Huang Z, et al. A fluorescent fiber pH sensor for sensitive, wide-range detection using orange-emitting silicon quantum dots[J]. Analytica Chimica Acta, 2025, 1368: 344330.

[46] Dingus O F, Grunlan M A. Leveraging Dynamic Electrostatic and Hydrophobic Interactions for Biomedical Hydrogels[J]. ACS Macro Letters, 2026, 15(4): 487.

[47] Feng S, Peng X, Deng Y, et al. Biomimetic nanozyme-decorated smart hydrogel for promoting chronic refractory wound healing[J]. ACS Applied Materials & Interfaces, 2024, 16(44): 59862-59879.

[48] Jain M, Trapani G, Trappmann B, et al. Stiffness modulation and pulsatile release in dual responsive hydrogels[J]. Angewandte Chemie International Edition, 2024, 63(22): e202403760.

[49] Li Z, Wang H, Zhang K, et al. Bisphosphonate-based hydrogel mediates biomimetic negative feedback regulation of osteoclastic activity to promote bone regeneration[J]. Bioactive materials, 2022, 13: 9-22.

[50] Zeng Z, Liu D, Li D, et al. An injectable double cross-linked hydrogel adhesive inspired by synergistic effects of mussel foot proteins for biomedical application[J]. Colloids and Surfaces B: Biointerfaces, 2021, 204: 111782.

[51] Yu T, Zhang L, Dou X, et al. Mechanically robust hydrogels facilitating bone regeneration through epigenetic modulation[J]. Advanced Science, 2022, 9(32): 2203734.

[52] Ni X, Zhao Y, Zhu J, et al. Hyaluronic acid methacryloyl-based co-delivery system for aflibercept and miR-21-3p antagomir: a dual-therapeutic approach for diabetic retinopathy[J]. Journal of Controlled Release, 2025: 114077.

[53] Xeroudaki M, Rafat M, Moustardas P, et al. A double-crosslinked nanocellulose-reinforced dexamethasone-loaded collagen hydrogel for corneal application and sustained anti-inflammatory activity[J]. Acta biomaterialia, 2023, 172: 234-248.

[54] Ding X, Yang B, Ni L, et al. Dual-Crosslinked Gelatin/Dextran Medical Hydrogels Based on Aldimine Condensation and Photopolymerization[J]. Gels, 2025, 11(11): 871.

[55] Zheng Y, Sun L, Zhai Z, et al. Wound microenvironment-responsive dually cross-linked nanofibrillar peptide hydrogels for efficient hemostatic control and multi-faceted wound management[J]. International Journal of Biological Macromolecules, 2024, 259: 129133.

[56] Yang S, Wu Y, Huang X, et al. Polyhexamethylene guanidine derived carbon dots with antibacterial and immunoregulatory properties loaded on carboxymethyl chitosan and ε-poly-L-lysine hydrogel to achieve sustained drug release for treating Pseudomonas aeruginosa infected wound[J]. Materials Today Bio, 2025: 102420.

[57] Qiao S, Chen W, Zheng X, et al. Preparation of pH-sensitive alginate-based hydrogel by microfluidic technology for intestinal targeting drug delivery[J]. International Journal of Biological Macromolecules, 2024, 254: 127649.

[58] Kopač T, Abrami M, Grassi M, et al. Polysaccharide-based hydrogels crosslink density equation: A rheological and LF-NMR study of polymer-polymer interactions[J]. Carbohydrate polymers, 2022, 277: 118895.

[59] Dong Y, Li H, Zou F, et al. Structure-properties correlations in low-methylated pectin hydrogels and aerogels crosslinked by divalent ions[J]. International Journal of Biological Macromolecules, 2025, 285: 137980.

[60] Hewawasam R S, Blomberg R, Šerbedžija P, et al. Chemical modification of human decellularized extracellular matrix for incorporation into phototunable hybrid-hydrogel models of tissue fibrosis[J]. ACS applied materials & interfaces, 2023, 15(12): 15071.

[61] Fu X, Xian H, Xia C, et al. Polymer homologue-mediated formation of hydrogel microneedles for controllable transdermal drug delivery[J]. International Journal of Pharmaceutics, 2024, 666: 124768.

[62] Mai Y, Wang H, Lu J, et al. Catalyst-modulated hydrogel dynamics for decoupling viscoelasticity and directing macrophage fate for diabetic wound healing[J]. Bioactive Materials, 2025, 52: 878-895.

[63] Sonthalia M, Jaiswal A K, Sadanandan S, et al. Highly tunable coconut shell lignin-gelatin crosslinked hydrogel for controlled drug delivery in wound healing[J]. International Journal of Biological Macromolecules, 2025: 148311.

[64] Lorenzo Lopez M, Kearns V R, Patterson E A, et al. Passive nanorheological tool to characterise hydrogels[J]. Nanoscale, 2025, 17(25): 15338-15347.

[65] Liu Y, Zhang J, Zhang Y, et al. Accelerated engineering of optimized functional composite hydrogels via High-throughput experimentation[J]. ACS Applied Materials & Interfaces, 2023, 15(45): 52908-52920.

[66] Lorke M, Kuth S, Frischknecht R, et al. Development of oxidized hyaluronic acid based hydrogels for neuronal tissue engineering: Effects of matrix stiffness on primary neurons[J]. Acta Biomaterialia, 2025.

[67] Dong Y C, Bouche M, Uman S, et al. Detecting and monitoring hydrogels with medical imaging[J]. ACS biomaterials science & engineering, 2021, 7(9): 4027-4047.