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Noncovalent Aggregation for Diverse Properties in Hydrogels: A Comprehensive Review

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ABSTRACT: The rapid expansion of hydrogel research over recent decades has bridged fundamental chemistry and physics with advanced materials science applications. This field necessitates comprehensive and in-depth review and discussion of the diverse and rapidly expanding body of research, thereby providing a cohesive understanding that can drive future innovations and applications. This review delves into the role of noncovalent interactions in hydrogel aggregation, a critical mechanism for creating desired microstructures that enhance material properties. Inspired by natural molecular architecture, this paper explores how synthetic hydrogels exploit hydrogen bonds, hydrophobic interactions, and other noncovalent forces to create robust, multifunctional, and water-rich networks. We further discuss methods to induce these interactions and the unique properties resulting from the formed structures. With these methods, we provide insights into the art of manipulating aggregated structures within hydrogels to develop adaptable, tunable materials for a broad range of applications, including bioengineering, robotics and soft electronics, highlighting their significant practical value across interdisciplinary fields.

CONTENTS

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1. INTRODUCTION

Hydrogel research has rapidly expanded from fundamental studies in chemistry and physics to broad-range applications in materials science over the past few decades (Figure 1A). The expansive growth stems from their unique combination of chemical, mechanical and physiological properties: hydrogels can retain large amounts of water within designed polymer architectures that resemble natural tissue,[1] enabling unparalleled performance in applications ranging from wound dressings,[2] tissue engineering,[3] matrix material for biomechanics research[4] to human-machine interfacing;[5] their porous structure facilitates controlled release of medications and rapid diffusion of ions and solvents, supporting applications in drug delivery,[6] desalination,[7] separation,[8] and energy storage;[9] and their responsiveness to environmental stimuli makes them ideal for smart materials from soft sensors to robotic actuators.[10] However, conventional hydrogels cross-linked by covalent bonds with pristine single polymer networks (i.e., without complex topology such as slide-ring or sufficient chain entanglement) face inherent trade-offs between critical properties—mechanical integrity versus mass transport,[11] strength versus toughness,[12] and swelling versus robustness[13]—limiting their performance in applications requiring balanced properties like flexible batteries and artificial muscles. In contrast, natural materials have evolved optimized structures through precise manipulation of interactions at multiple length scales,[14] creating self-assembled architectures under mild conditions that dynamically respond to stimuli, provide structural support, and self-repair.[15]

The formation of natural materials with superior properties and functionalities relies on a cascade of intricately controlled noncovalent interactions that lead to programmed aggregations.[16] These interactions, often triggered by specific stimuli such as temperature fluctuations,[17] light illumination,[18] or variations in ionic strength and pH,[19] facilitate the aggregation of biomonomers and macromolecules through mechanisms like hydrogen bonding, hydrophobic interactions, and ionic interactions.[20] Under these mild and precise conditions, biological building blocks self-assemble into unique structures—such as pores, fibrils, and hierarchical networks—tailored for specific functional needs:[21] porous structures enhance rapid nutrient transport,[22] fibrillar formations provide high load-bearing capacity,[23] and hierarchical networks offer multifunctionality.[24] A notable example is DNA, which aggregates by wrapping around histone proteins to form chromatin, further coiling into compact chromosomes for efficient genetic information transmission[25] (Figure 1B). Inspired by these natural architectures, researchers have addressed hydrogel material challenges by fine-tuning noncovalent interaction-induced aggregation.[26] For instance, Hua et al. tackled the strength-toughness trade-off by constructing hierarchical structures through ice templating and salting-out effects, achieving hydrogels with ultrahigh ultimate stress (23.5 ± 2.7 MPa), strain (2900 ± 450%), and toughness (210 ± 13 MJ/m^3) through mechanisms operating at multiple length scales.[27] Similarly, Alsaid et al. enhanced both mechanical strength and mass transport through hydrophobic interaction-enabled hierarchically porous hydrogels, exhibiting twice the swelling ratio and Young's modulus, and six times the deswelling rate compared to conventional methods.[28] Other innovative properties achieved through noncovalent interaction-induced aggregation include exceptional wet adhesion (~1268 J/m^2 adhesion strength)[29] and tunable ionic conductivity (~10 mS/cm).[30] This approach excels in tuning hydrogel properties due to the reversible and dynamic nature of noncovalent bonds[31] and the numerous possibilities for forming physical interactions between different functional groups,[32] enabling facile modulation under mild fabrication conditions. While alternative strategies using covalent chemistry (such as slide ring hydrogels and tanglemers) exist, they have been extensively discussed elsewhere and fall outside this review's scope.[33−35]

In culminating the exploration of noncovalent aggregation for diverse properties in hydrogels, we provide in this review a systematic summary of the noncovalent interaction classification, processing methods, and structural optimizations leading to property enhancements of hydrogels (Figure 2). We specifically emphasize the foundational mechanisms that define processing-structure and structure−property relationships. Through examining the sets of hydrogel properties demanded by major applications, we then discuss how this knowledge was exploited to craft hydrogels with tailored properties. The core focus of this review is the exploration of how noncovalent interactions regulate molecular chain aggregation in hydrogels, directly influencing their microstructure and resulting properties. By adopting this mechanism-first approach, we systematically analyze the fundamental principles governing how diverse noncovalent forces drive aggregation across various hydrogel systems and construct a framework for understanding structure−property relationships, providing more versatile discussion than other insightful hydrogel-based reviews of specific polymer compositions or applications.[36−38] Ultimately,

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Chem. Rev. XXXX, XXX, XXX−XXX

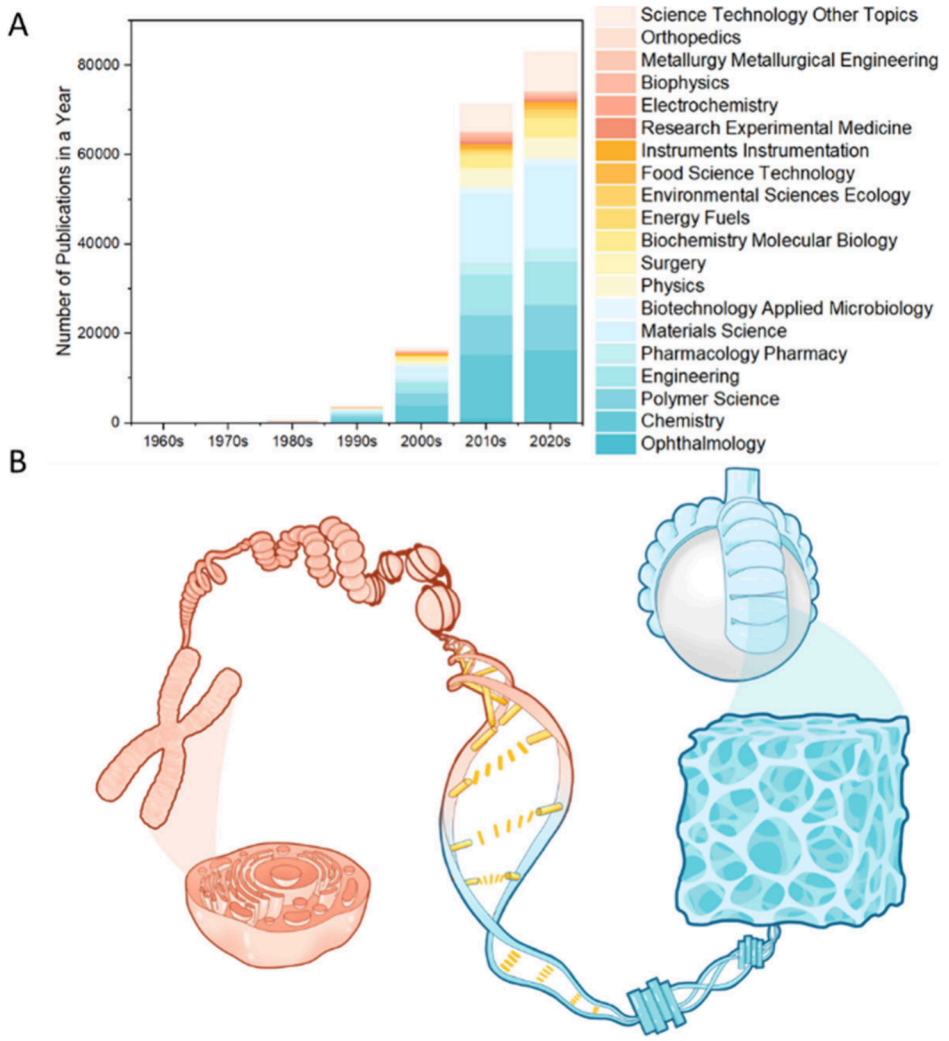

Figure 1. (A) Number of publications in various fields of hydrogels over the past few decades. (B) Synthetic hydrogel materials developed from bioinspiration of natural materials.

we project into the future of hydrogel research, focusing on how controlled noncovalent aggregation could solve outstanding challenges to realize adaptable, tunable materials for an array of applications, spanning from drug delivery to tissue engineering, and from sensory technologies to soft robotics and electronics.

2. NONCOVALENT INTERACTIONS

Noncovalent interactions play a pivotal role in dictating the structure, functionality, and overall performance in both naturally occurring and man-made hydrogels (Figure 3).[39] In living systems, an array of noncovalent interactions such as hydrogen bonding, hydrophobic interactions, and ionic interactions works cooperatively to sustain the structural and functional dynamics of the biological components.[20] Since these interactions are largely associated with the presence of corresponding functional groups, synthetic hydrogels bearing similar groups—such as those made from polyether,[40] polyesters[41] and vinyl polymers[42]—can mimic the versatile properties of natural materials. Interestingly, similar property enhancing strategies based on noncovalent interactions have also been successfully employed in other soft materials such as ionogels, organogels and elastomers, where physical cross-linking and reversible bonding contribute to enhanced performance and functionality.[43] Understanding the chemical origin of these various noncovalent interactions is crucial for designing hydrogels with tailored properties, requiring careful consideration to balance stability and functionality by adopting appropriate interactions with optimal bond strength and reversibility. To gain systematic understanding, we classify these interactions based on their interaction strength and type, summarizing natural and synthetic hydrogels exhibiting these interactions, their applications, and the functional groups involved in Table 1, with a comprehensive overview of their bond characteristics in Table 2.

2.1. Strong Noncovalent Interactions

Noncovalent interactions involving electron transfer typically form stronger bonds in hydrogel networks, though they require combining dissimilar components within the structure.[78] In hydrogels, ionic interactions occur through electrostatic attraction between oppositely charged ions, significantly contributing to network cross-linking and stability. These interactions commonly involve carboxylate groups,[79] sulfonate groups,[80] and ionic liquid moieties[81] present on polymer chains, with metal ions often applied to modulate the interaction strength.[82] For instance, alginate — a natural polysaccharide, forms ionic cross-links with divalent cations

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Chem. Rev. XXXX, XXX, XXX−XXX

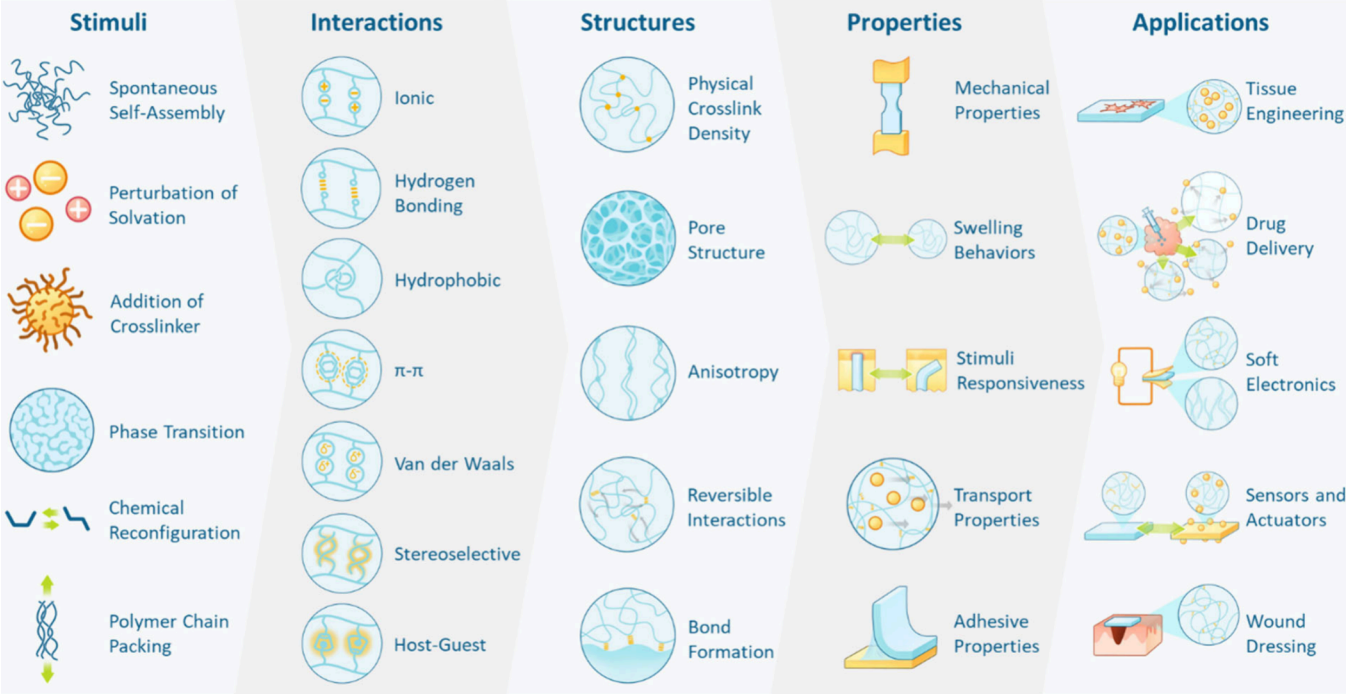

Figure 2. Structure overview of the review paper.

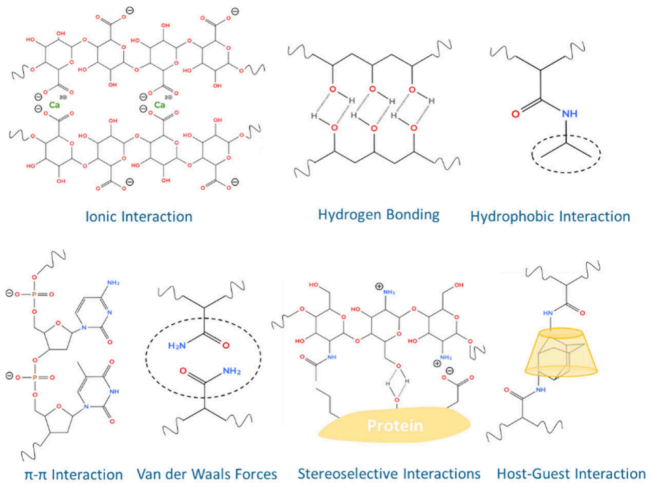

Figure 3. Representative examples of noncovalent interactions in aggregated hydrogel networks. These include ionic interactions between alginate chains and calcium ions; hydrogen bonding between poly(vinyl alcohol) (PVA) chains; hydrophobic interactions in poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels; π-π interactions in DNA-based hydrogels; van der Waals forces between polyacrylamide (PAAm) chains; Stereoselective interactions between chitosan and proteins; and host−guest interactions involving cyclodextrin-functionalized hydrogels.

like calcium, facilitating gel formation.[48] Synthetic hydrogels such as poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) utilize sulfonic acid groups to create networks with high hydrophilicity and sensitivity to ionic strength.[65] Ionic interactions provide strong cross-linking and enhance the mechanical properties of hydrogels at neutral conditions. However, due to the water infused nature of hydrogels, changes in the ionic strength[83] or pH[84] can significantly alter their properties. The reversible cross-linking of oppositely charged moieties under dynamic conditions makes them useful for applications in environmental remediation and controlled drug release.[85] However, the presence of metal ions can sometimes introduce toxicity concerns, requiring careful selection and control of the ion types.[86]

2.2. Weak Noncovalent Interactions

The weaker noncovalent interactions do not involve electron transfer and could be formed when the functional groups come into proximity. Hydrogen bonding, a type of dipole−dipole interaction, is commonly utilized in both natural and synthetic hydrogels.[87] Hydrogen bonds occur between a hydrogen atom that is covalently bonded to a highly electronegative atom (e.g., nitrogen, oxygen, or fluorine) and another electronegative atom. Functional groups such as hydroxyl,[88] carbonyl,[89] amine,[90] and carboxyl[91] are often involved in hydrogen bonding. For instance, in natural hydrogels such as cellulose and chitin, hydrogen bonding could form between abundant hydroxyl groups, leading to the formation of long and strong fibrils that contribute to their structural integrity and mechanical properties.[44,45] Similarly, in synthetic hydrogels such as poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAA), hydrogen bonding could form between hydroxyl or carboxyl groups to form interconnected networks with tunable properties.[49,51] Hydrogen bonding provides significant structural enhancement and mechanical strength to hydrogels, yet they are often sensitive to environmental conditions like pH[92] and temperature,[93] which may limit their stability in varying conditions. These bonds typically fail at elevated temperatures that provide sufficient energy to overcome the bond strength, in the presence of polar solvents that compete for hydrogen bonding sites, or when pH changes alter the protonation state of functional groups. Due to their moderate strength and reversibility, hydrogen bonds are particularly suitable for tissue engineering scaffolds, self-healing hydrogels, and biomedical adhesives. In practice, a sufficiently high number density of hydrogen bonding is needed to meet the stability and strengthening requirements.

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Chem. Rev. XXXX, XXX, XXX−XXX

Table 1. Noncovalent Interactions and Applications of Natural and Synthetic Hydrogels

Interaction Type	Material Type	Material	Functional Groups	Applications	Ref
Hydrogen Bonding	Natural	Cellulose	Hydroxyl group	Filtration and water purification. Biodegradable packaging materials. Tissue engineering scaffolds.	44
		Chitin	Hydroxyl group, carbonyl group	Wound dressings and healing agents. Drug delivery systems. Antibacterial coatings.	45
		Proteins	Carbonyl group, amide group	Skin regeneration and cosmetic products. Scaffolds for tissue engineering. Controlled drug release systems.	46
		DNA/RNA	Hydroxyl groups, nitrogenous bases, phosphate groups	Biosensors and diagnostics. Gene therapy vectors. Programmable nanostructures in nanotechnology.	47
		Alginate	Hydroxyl groups	Drug encapsulation and delivery. Scaffolding in tissue engineering. Wound healing and dressings.	48
	Synthetic	Poly(vinyl alcohol) (PVA)	Hydroxyl groups	Contact lenses. Drug delivery systems. Artificial cartilage and tissue scaffolds.	49
		Poly(methacrylic acid) (PMAA)	C═O (carbonyl)	Smart drug delivery systems responsive to pH. Coatings for controlled release. Hydrogels for tissue regeneration.	50
		Poly(acrylic acid) (PAA)	C═O (carbonyl)	Superabsorbent polymers in hygiene products. Agricultural water retention agents. pH-responsive drug delivery systems.	51
		Poly(*N*-vinylpyrrolidone) (PVP)	C═O (carbonyl)	Wound healing gels. Blood plasma expanders. Adhesives and coatings in medical devices.	52
		Polyethylene Glycol (PEG)	Ether	Drug delivery vehicles. Tissue engineering scaffolds. Surface modifiers for biocompatibility.	53
		Polyurethane	Urethane linkages	Flexible coatings and adhesives. Biomedical foams for wound healing. Vascular grafts and soft electronics.	54
		Poly(acrylamide) (PAAm)	Amide groups	Water treatment. Tissue engineering. Sensors and actuators.	55
Hydrophobic Interactions	Natural	Proteins	Aliphatic side chains, Proline	Skin regeneration and cosmetic products. Scaffolds for tissue engineering. Controlled drug release systems.	46
		Polysaccharides (Methylcellulose)	Methylation groups	Food industry. Tissue engineering. Biomedical coatings.	56

https://doi.org/10.1021/acs.chemrev.5c00069
Chem. Rev. XXXX, XXX, XXX−XXX

Table 1. continued

Interaction Type	Material Type	Material	Functional Groups	Applications	Ref
	Synthetic	Poly(*N*-isopropylacrylamide) (PNIPAM)	Isopropyl groups	Temperature-responsive drug delivery systems. Smart actuators for soft robotics. Biosensors.	57
		Poly(vinyl acetate) (PVAc)	Acetate groups	Adhesives. Drug delivery. Cement additives.	58
		Polyurethane	Aliphatic or aromatic groups	Flexible coatings and adhesives. Biomedical foams for wound healing. Vascular grafts and soft electronics.	54
		Pluronic or poloxamer hydrogels	PPO blocks	Tissue engineering. Wound healing. Cosmetics.	59
Ionic Interactions	Natural	Alginate	Carboxylate groups with positively charged ions	Drug encapsulation and delivery. Scaffolding in tissue engineering. Wound healing and dressings.	48
		Chitosan	Amino groups	Antimicrobial coatings and food preservation. Drug delivery and controlled release systems. Water treatment	60
		Hyaluronic Acid	Carboxylate groups and hydroxyl groups	Dermal fillers in cosmetics. Cartilage repair and joint lubrication. Drug delivery in ophthalmology.	61
		Carrageenan	Sulfate groups with positively charged ions	Gelling and thickening agent in food. Stabilizer in pharmaceutical formulations. Delivery systems for bioactive compounds.	62
		Pectin	Carboxylate groups with positively charged ions	Drug delivery systems. Food gelling agent. Encapsulation of probiotics.	63
		Gellan Gum	Carboxylate groups of glucuronic acid residues with positively charged ions	Thickener and stabilizer in food products. Scaffolds for tissue engineering. Controlled-release drug delivery systems.	64
	Synthetic	Poly(acrylic acid) (PAA)	Carboxylate groups with positively charged ions	Superabsorbent polymers in hygiene products. Agricultural water retention agents. pH-responsive drug delivery systems.	51
		Poly(methacrylic acid) (PMAA)	Carboxylate groups with positively charged ions	Smart drug delivery systems responsive to pH. Coatings for controlled release. Hydrogels for tissue regeneration.	50
		Poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS)	Sulfonate groups	Biomedical devices. Soft robotics actuators. Electrochemical sensors.	65
		Poly(ionic liquid) Hydrogels	Ionic liquid moieties	Separation membranes. Electrochemical devices. Responsive soft materials.	66

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Chem. Rev. XXXX, XXX, XXX−XXX

Table 1. continued

Interaction Type	Material Type	Material	Functional Groups	Applications	Ref
Stereoselective Interactions	Natural	DNA	Stereospecific base-pairing (A-T, G-C)	Biosensors and diagnostics. Gene therapy vectors. Programmable nanostructures in nanotechnology.	47
		Protein	Specific amino acid sequences	Skin regeneration and cosmetic products. Scaffolds for tissue engineering. Controlled drug release systems.	46
	Synthetic	Peptide-based Hydrogels	Chiral amino acid residues	Biocatalysis and biosensors. Drug delivery. Injectable scaffolds for tissue engineering.	67
		Hydrogels with Cyclodextrin	Cyclodextrins	Controlled drug delivery systems. Sensing and molecular recognition. Water purification and pollutant removal.	68
π-π Interactions	Natural	Melanin-containing Hydrogels	Aromatic structure	Biomedical imaging. Tissue engineering. Photocatalysis.	69
		DNA	Aromatic nucleobases	Biosensors and diagnostics. Gene therapy vectors. Programmable nanostructures in nanotechnology.	47
		Protein	Aromatic amino acid residues	Skin regeneration and cosmetic products. Scaffolds for tissue engineering. Controlled drug release systems.	46
	Synthetic	Polyaniline (PANI)-based Hydrogels	Conjugated aromatic structure of the polyaniline backbone	Electrochemical sensors. Conductive hydrogels for energy storage. Actuators and flexible electronics.	70
		Polyphenylenevinylene (PPV)	Alternating single and double bonds in its backbone	Optoelectronics. Sensors. Electrochromic devices.	71
		Polythiophene (PTh)-based hydrogels	Alternating single and double bonds in its backbone	Sensors for environmental monitoring. Electrochromic devices. Soft actuators for robotics.	72
		Poly(3,4-ethylenedioxythiophene) (PEDOT)-based Hydrogel	Alternating single and double bonds in its backbone	Bioelectronics. Energy storage. Electrochemical devices.	73
Host–Guest interactions	Synthetic	Hydrogels with Cyclodextrin	Cyclodextrin	Controlled drug delivery systems. Sensing and molecular recognition. Water purification and pollutant removal.	68
		Hydrogels with Pillar[n]arenes	Pillar[n]arenes	Sensing. Water purification. Molecular recognition.	74
		Metal–organic framework (MOF)-integrated hydrogels	MOFs	Gas storage and separation. Catalysis. Advanced drug delivery systems.	75
van der Waals forces	Natural	Agarose	Hydroxyl groups	Gel electrophoresis for DNA/RNA separation. Cell culture matrices. Tissue engineering hydrogels.	76

https://doi.org/10.1021/acs.chemrev.5c00069
Chem. Rev. XXXX, XXX, XXX−XXX

Table 1. continued

Interaction Type	Material Type	Material	Functional Groups	Applications	Ref
		Alginate	Carboxyl groups and hydroxyl groups	Drug encapsulation and delivery. Scaffolding in tissue engineering. Wound healing and dressings.	48
		Chitosan	Amino groups and hydroxyl groups	Antimicrobial coatings and food preservation. Drug delivery and controlled release systems. Water treatment	60
	Synthetic	Poly(vinyl alcohol) (PVA)	Hydroxyl groups	Contact lenses. Drug delivery systems. Artificial cartilage and tissue scaffolds.	49
		Polyethylene Glycol (PEG)	Ether groups and terminal hydroxyl groups	Drug delivery vehicles. Tissue engineering scaffolds. Surface modifiers for biocompatibility.	77
		Poly(acrylamide) (PAAm)	Amide groups	Water treatment. Tissue engineering. Sensors and actuators.	55

Noncovalent interactions could also take place between functional groups bearing atoms of low electronegativity differences, such as hydrophobic interactions, π-π stacking and van der Waals forces. Among them, hydrophobic interactions are entropically driven and induced by the tendency of nonpolar regions within polymers to phase separate from water, leading to the aggregation of polymer chains.[94] In natural hydrogels, hydrophobic amino acids in proteins contribute to the formation of structured networks.[46] Synthetic hydrogels may incorporate hydrophobic components such as hydrocarbons and fluorocarbons to control swelling behavior and mechanical strength.[57−59] Polymers like poly(*N*-isopropylacrylamide) (PNIPAM) exploit hydrophobic interactions among isopropyl groups to exhibit temperature-responsive behavior.[95] Hydrophobic interactions are highly sensitive to temperature and solvent polarity,[96] with failure typically occurring at low temperatures (for lower critical solution temperature (LCST) thermoresponsive systems), in the presence of organic solvents that disrupt the water structure, or upon addition of surfactants that can solubilize hydrophobic domains. These characteristics make hydrophobic interaction-based hydrogels suitable for thermoresponsive materials, drug encapsulation systems, and controlled release applications. However, the aggregation of hydrophobic regions can sometimes lead to reduced hydrophilicity and potential difficulties in drug delivery applications.

For π-π stacking, aromatic groups are involved in driving the aggregation of molecules in hydrogels.[97] Natural hydrogels containing melanin or DNA leverage these interactions for enhanced electrical conductivity or molecular recognition.[46,47,69] Synthetic hydrogels like polyaniline (PANI)-based and polythiophene (PTh)-based hydrogels exploit π-π interactions between aromatic rings for applications in sensors and electronic devices.[70−73] π-π stacking interactions can impart unique electronic properties to hydrogels, making them suitable for applications in sensors and electronic devices.[98] These interactions are particularly sensitive to solvent polarity, with failure conditions including exposure to aromatic solvents that compete for π-π interactions. The distinctive properties of π-π interactions make them ideal for conductive hydrogels, biosensors, and electronic sensing devices. However, the reliance on specific aromatic groups can limit the diversity of polymers that can be used in these hydrogels.

van der Waals forces are often overlooked in the structural engineering of hydrogels due to their weak interactions, yet they play a significant role in maintaining the structural integrity of large molecules like proteins and polymers.[76] van der Waals forces include weak intermolecular attraction and repulsion forces between atoms, molecules, and surfaces. These forces are sensitive to temperature and distance between interacting molecules, with failure typically occurring at elevated temperatures that increase molecular motion or when molecular separation increases beyond the effective range of these forces. While typically serving as supporting interactions in most hydrogel systems rather than primary design elements, van der Waals forces contribute to the overall stability and mechanical properties across virtually all hydrogel types. There are three main types of van der Waals forces, namely dispersion forces (London forces), dipole−dipole interactions and dipole−induced dipole forces.[99]

2.3. Mixed Noncovalent Interactions in Hydrogels

Beyond individual noncovalent interactions, real-world hydrogel systems rarely rely on a single interaction type. Instead, they leverage combinations of multiple interaction types that can either work synergistically or compete within the polymer network. Understanding these complex interplays is crucial for designing hydrogels with optimized performance characteristics, as they directly impact the material's structural organization, mechanical properties, and responsive behavior. This section provides a conceptual foundation for understanding how different noncovalent forces interact when present simultaneously within hydrogel systems.

2.3.1. Synergy and Competition between Different Interactions. When different noncovalent interactions coexist in a hydrogel network, their combined effect rarely represents a simple additive relationship. Instead, these interactions can either enhance each other or interfere with one another, significantly impacting the overall material properties. To

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Chem. Rev. XXXX, XXX, XXX−XXX

Table 2. Comparative Analysis of Noncovalent Interactions in Hydrogels

Interaction Type	Interaction Strength	Environmental Sensitivity	Typical Failure Conditions	Suitable Applications	Functional Groups Involved	Ref
Ionic Interactions	5−200 kJ/mol	pH, Ionic strength, Temperature	High ionic strength, Extreme pH, Competing ions	Stimuli-responsive hydrogels, Drug delivery systems, Self-healing materials	Carboxylate, Sulfonate, Ammonium, Phosphate groups; Metal ions	100−102
Hydrogen Bonding	10−20 kJ/mol	Temperature, pH, Solvent polarity	Elevated temperatures, pH changes beyond functional group pK_a, Polar solvents	Tissue engineering, Self-healing hydrogels, Biomedical adhesives	Hydroxyl, Carboxyl, Amino, Amide, Carbonyl groups	103−105
Hydrophobic Interactions	1−40 kJ/mol	Temperature, Solvent polarity, Surfactants	Low temperatures (<LCST), Organic solvents, Surfactant addition	Thermoresponsive materials, Drug encapsulation, Controlled release	Alkyl chains, Aromatic groups, Fluorinated segments	106−108
π-π Interactions	5−45 kJ/mol	Solvent polarity	Aromatic solvents	Conductive hydrogels, Sensors, Biosensors	Aromatic rings, Conjugated structures	109−111
van der Waals Forces	0.04−0.7 μJ/m^2	Temperature, Pressure, Distance	Elevated temperatures, Increased distances	Supporting interactions in most hydrogels	All types of molecules	112, 113
Host−Guest Interactions	10−50 kJ/mol	pH, Competitive guests, Temperature	Competing guest molecules, Extreme pH, High temperatures	Drug delivery, Molecular recognition, Stimuli-responsive systems	Cyclodextrins, Crown ethers, Calixarenes	114−116
Stereoselective Interactions	4−10 kJ/mol	Temperature, pH, Solvent polarity	Racemization conditions, Structural deformation	Chiral separation, Highly specific drug delivery	Chiral centers, Stereoisomers	117−119

rationally harness synergy or mitigate competition, one must first identify the target property and then map out which microstructural features best deliver that performance. From there, selecting an appropriate design strategy can position multiple interactions in ways that reinforce rather than antagonize each other. Thus, by matching "desired property → required microstructure → design strategy", researchers can systematically integrate different noncovalent interactions to maximize synergy and minimize unwanted competition.

The combination of hydrogen bonding with π-π stacking in hydrogels containing both polar functional groups and aromatic moieties illustrates a synergistic relationship. In such systems, hydrogen bonds typically contribute to initial structural integrity and elasticity, while π-π interactions provide additional strength and energy dissipation mechanisms.[97] Xu et al. demonstrated that in small-molecule gelators containing both amide groups (hydrogen bonding) and aromatic units (π-π stacking), the two interaction types operate at different length scales and under different deformation regimes, creating a hierarchical reinforcement system that results in superior mechanical strength and self-healing properties.[120]

However, when ionic interactions are introduced into hydrogen-bonded networks, competitive effects often emerge. For instance, in polyelectrolyte hydrogels exposed to high salt concentrations, the screening effect of ions can disrupt existing hydrogen bonds by competing for polar interaction sites. Conversely, at intermediate ionic strengths, the introduction of ionic cross-links can actually strengthen hydrogen-bonded networks by reducing electrostatic repulsion between polymer chains, allowing for closer chain packing and enhanced intermolecular hydrogen bonding. This complex relationship between ionic and hydrogen bonding interactions highlights the importance of careful parameter optimization in multi-cross-link systems.

The pairing of electrostatic interactions with hydrophobic associations represents another powerful synergistic combination. In the double-network hydrogels pioneered by Gong et al., charged networks provide structural integrity while hydrophobic domains create sacrificial bonds that dissipate energy under stress.[121] Sun et al. further demonstrated this principle in polyampholyte hydrogels, where the random distribution of positive and negative charges creates ionic bonds of varying strengths that work in concert with hydrophobic interactions to achieve remarkable toughness and viscoelasticity.[122] The key to this synergy lies in the distinct dissociation energies and kinetics of the different bond types, which allow them to respond to mechanical stress at different strain thresholds.

2.3.2. Specialized Mixed Interaction Systems in Nature and Synthetic Materials. Beyond simple combinations of fundamental interactions, nature has evolved sophisticated systems where multiple noncovalent forces work in concert to achieve unique functionalities. Synthetic materials increasingly mimic these complex interaction networks to achieve advanced properties. Two particularly notable examples of such specialized mixed interaction systems are stereoselective interactions and host−guest interactions, which themselves often involve multiple fundamental forces working in concert.

Stereoselective interactions rely on the spatial complementarity between interacting molecules, utilizing a precise arrangement of multiple noncovalent bonds—typically combinations of hydrogen bonds, van der Waals forces, and

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Chem. Rev. XXXX, XXX, XXX−XXX

sometimes π-π interactions.[123] In DNA hydrogels, the stereospecific base-pairing involves both hydrogen bonding patterns and π-π stacking between complementary nucleobases.[46,47] The synergistic effect emerges because these different interactions reinforce each other in a cooperative manner—hydrogen bonds provide directionality and specificity, while π-π stacking contributes additional stability through electronic interactions.[124,125] This cooperative action creates binding strengths far exceeding what either interaction type could achieve independently. For instance, in DNA double helices, the hydrogen bonding between base pairs alone would be insufficient for stability at physiological temperatures, but when combined with the stacking interactions between adjacent bases, they create a remarkably stable structure.[126] Stereoselective interactions are particularly sensitive to temperature and solvent polarity, which can alter the three-dimensional conformation of the interacting molecules. Typical failure conditions include racemization processes, structural deformation of the chiral molecules, and changes in solvent properties that affect the spatial arrangement of stereoisomers. Given their high specificity, stereoselective interactions are especially suitable for chiral separation applications, targeted drug delivery systems,[127] and biomimetic materials where molecular recognition must be highly selective.[128] However, these interactions can be complex to design and control, requiring precise molecular engineering.

Host−guest interactions represent a more sophisticated form of mixed noncovalent bonding.[129] Cyclodextrin-polymer hydrogels exemplify this approach, where the hydrophobic cavity of cyclodextrin hosts interacts with guest molecules through a combination of hydrophobic effects, van der Waals forces, and sometimes hydrogen bonding at the cavity rim.[68,74] The synergistic nature of these interactions manifests in what chemists call the "high-affinity binding paradox"—individually weak interactions collectively generate binding constants orders of magnitude higher than predicted by their individual contributions. This amplification occurs because the initial binding events preorganize the system, reducing the entropic penalty for subsequent interactions and creating a positive cooperative effect. For example, when a hydrophobic guest molecule enters the cyclodextrin cavity, the resulting conformational change can position hydrogen bonding sites at the cavity rim in optimal orientation for additional bonding, creating a self-reinforcing binding process.[130] The binding affinity in these systems can be finely tuned by modifying either the host cavity or the guest molecule structure. These interactions show significant sensitivity to pH changes that can alter the ionic state of the host or guest molecules, the presence of competitive guest molecules that can displace the intended guest, and temperature fluctuations that affect binding affinity. Failure typically occurs when competing molecules with higher affinity displace the guest, when extreme pH conditions alter the host cavity structure, or at elevated temperatures that provide sufficient energy to overcome the binding forces. Host−guest systems are particularly well-suited for stimuli-responsive drug delivery systems[131] and analyte sensing applications.[132] However, the efficiency of these interactions depends on the compatibility between host and guest molecules, which may require extensive optimization.

The strategic combination of different noncovalent interactions in hydrogel design represents a frontier in materials science, enabling the creation of systems with enhanced mechanical properties, multiresponsive behavior, and self-regulating capabilities that more closely mimic the sophisticated functionality of biological materials. Section 3 will explore how various fabrication and processing methods can be used to induce and control these mixed interaction systems in practice.

3. METHODS TO INDUCE AGGREGATION

Having established the fundamental types and characteristics of noncovalent interactions in hydrogel systems, we now turn our attention to the practical methods that can be employed to induce and control these interactions. The following section explores specific techniques that leverage different noncovalent forces to create aggregated structures in hydrogels. Each method described below has particular efficacy in triggering or enhancing certain types of noncovalent interactions, resulting in distinctive structural outcomes and material properties.

Hydrogels used in applications of bioengineering,[133] flexible electronics,[134] soft robotics[135] and water purification[136] often require optimized mechanical,[137] swelling,[138] transport,[139] stimuli responsive[140] and adhesive properties[141] that are not readily achievable by covalent interactions alone. The noncovalent interactions described in Section 2 provide the chemical foundation for these properties, but they must be deliberately induced and controlled through specific processing methods to achieve desired structural and functional outcomes. The strategic selection of aggregation methods is crucial because each technique preferentially triggers or enhances particular types of noncovalent interactions. For instance, solvent perturbation methods like cosolvent addition predominantly affect hydrogen bonding and hydrophobic interactions, while ionic cross-linking primarily leverages electrostatic forces.[142] Understanding these relationships enables researchers to precisely engineer hydrogel properties by selecting methods that activate the most beneficial interactions for a specific application. In general, the occurring interactions need to be strong enough to result in chain aggregations, which further leads to structural evolutions tied to property enhancements.[143] As we pivot from understanding the natural and inherent interactions within hydrogels to the methods of inducing aggregation, we bridge the gap between passive material behavior and active material manipulation.

The methods used to induce aggregation in hydrogels are underpinned by fundamental kinetic and thermodynamic principles that dictate how these materials respond to various stimuli. To ensure that aggregation acts favorably in optimizing the material's properties, the precursor/hydrogel must remain stable until reaching a terminal reaction state where aggregation by noncovalent interaction is allowed to take place via perturbation of its thermodynamic equilibria.

From a thermodynamic perspective, the phase-field model based on Flory−Rehner theory, provides a framework for understanding the processes of polymer aggregation in solvents with the possibility of having phase separation, including the driving forces, conditions, and governing factors.[144,145] In a single-phase system with homogeneous polymer and solvent concentration, the free energy determines the equilibrium state of a swelled hydrogel, which is composed of two terms: elastic energy and the energy of mixing.[146,147] The free energy density can be expressed as

$$W = W_e + W_m \tag{1}$$

The equation for free energy density of elastic energy, assuming a compressible polymer network, is

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Chem. Rev. XXXX, XXX, XXX−XXX

$$W_e = \frac{1}{2}NkT[I_1 - 3 - 2\ln J] + \frac{\kappa}{2}(J - \nu C - 1)^2 \quad (2)$$

, where N is the number of cross-links per unit volume of the hydrogel in the dry state, k is the Boltzmann constant, T is the absolute temperature, I_1 is the first invariant of the deformation gradient tensor, relating to strain, J is the determinant of the deformation gradient tensor of the hydrogel, representing the volume change due to the deformation, k is the bulk modulus, C is the number of solvent molecules per unit reference volume, and ν is the volume of a solvent molecule. The deformation elastic energy of the polymer chains in the network is described by the first term, while the second term addresses the volumetric compression or expansion of the polymer network, penalizing deviations from the natural volume.

The equation for free energy density of mixing is

$$W_m = \frac{kT}{\nu}\left(\nu C \ln\frac{\nu C}{\nu C + 1} + \chi\frac{\nu C}{\nu C + 1}\right) \quad (3)$$

, where χ is the Flory–Huggins interaction parameter between polymer and solvent. The first term represents entropy of mixing, which is a measure of the increase of randomness when components are mixed. Polymers, being large molecules, contribute less to the entropy of mixing compared to smaller solvent molecules. This is because mixing a large polymer with a solvent result in fewer possible configurations than mixing small molecules. As a result, the entropy contribution to the free energy of mixing is generally lower for polymers. The third term represents internal energy between polymer segments and the molecules of the solvent. This is represented by the Flory–Huggins interaction parameter, χ, which reflects the nature of the interaction. If the interaction between the polymer and solvent is favorable (χ is small or negative), the polymer will tend to remain well-dissolved. Conversely, if the interaction is unfavorable (χ is large and positive), the system's free energy increases. This term takes the noncovalent interaction into account.

The total free energy G of a system containing polymer and the solvent it swells can be plotted against polymer concentration ϕ to illustrate the effect of stimuli on the thermodynamic aspect of the system, as depicted in Figure 4. The polymer concentration is related to the number of solvent molecules per unit reference volume as

$$\phi = \frac{1}{\nu C + 1} \quad (4)$$

In the exemplary LCST type phase diagrams, the binodal and spinodal curves mark the boundaries between one phase, metastable, and unstable regions. The tendency of aggregation and phase separation will be determined by the shape of the binodal and spinodal curves, temperature, and polymer concentration. When stimuli (solvent, ions, cross-linker, etc.) are added to a system or the environment (temperature, illumination, etc.) of the system is changed, the phase diagram and the free energy curve will change. Aggregation will happen if the polymer concentration for minimum free energy is shifted to a higher value than the current polymer concentration. In some cases, the interaction parameter is increased to a point where a second local minimum of free energy appears. The system will phase separate into polymer rich and polymer poor phases corresponding to the two local minimum. There are two mechanisms for phase separation,

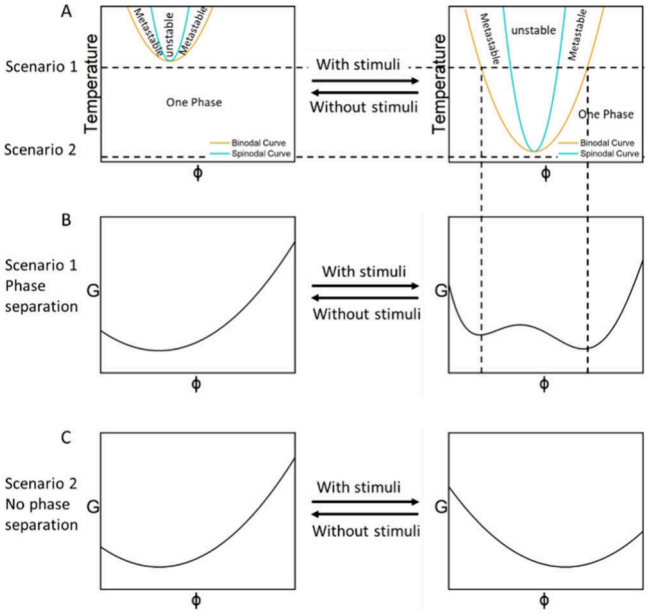

Figure 4. Phase diagrams and free energy curves for aggregation processes with or without phase separation. (A) Temperature–composition phase diagram showing the binodal curve that separates the one-phase and two-phase regions, and the spinodal curve that separates the metastable and unstable regions. (B) Free energy (G) versus polymer concentration (ϕ) curves illustrating Scenario 1 where phase separation occurs. Left panel shows the system without stimuli having a single minimum, representing a stable one-phase system. Right panel shows the same system after applying stimuli, resulting in a curve with two minima, indicating phase separation into polymer-rich and polymer-poor domains. The vertical dashed lines mark the equilibrium concentrations of the two coexisting phases. (C) Free energy (G) versus polymer concentration (ϕ) curves illustrating Scenario 2 where no phase separation occurs despite polymer aggregation. Left panel shows the initial system with a single free energy minimum. Right panel shows how applying stimuli shifts the position of the minimum toward higher polymer concentration but maintains a single-minimum curve.

namely spinodal decomposition that occurs inside the unstable region and nucleation-and-growth that happens inside the metastable region.

When phase separation happens, another contribution from the coherent interface between dissimilar phases will be added to the total energy density of the system, which can be expressed as

$$W_i = \frac{\eta}{2}JH_{iK}\frac{\partial C}{\partial X_K}\frac{\partial C}{\partial X_L}H_{iL} \quad (5)$$

Where η is interfacial tension parameter. It describes how much energy is associated with the concentration gradient at the interface. H_{iK} and H_{iL} are components of a metric tensor or a related geometric tensor. They represent the curvature and geometry of the interface. $\frac{\partial C}{\partial X_K}$ and $\frac{\partial C}{\partial X_L}$ are spatial gradients of concentration in the polymer solution with respect to spatial coordinates X_K and X_L. These terms describe how concentration inhomogeneities contribute to the interfacial energy. This W_i term quantifies the energy required to maintain an interface between phases or regions of different concentration.

From a kinetic perspective, factors such as the triggering stimuli, molecular mobility, diffusion rates, and interaction dynamics all contribute to the determination of the aggregation

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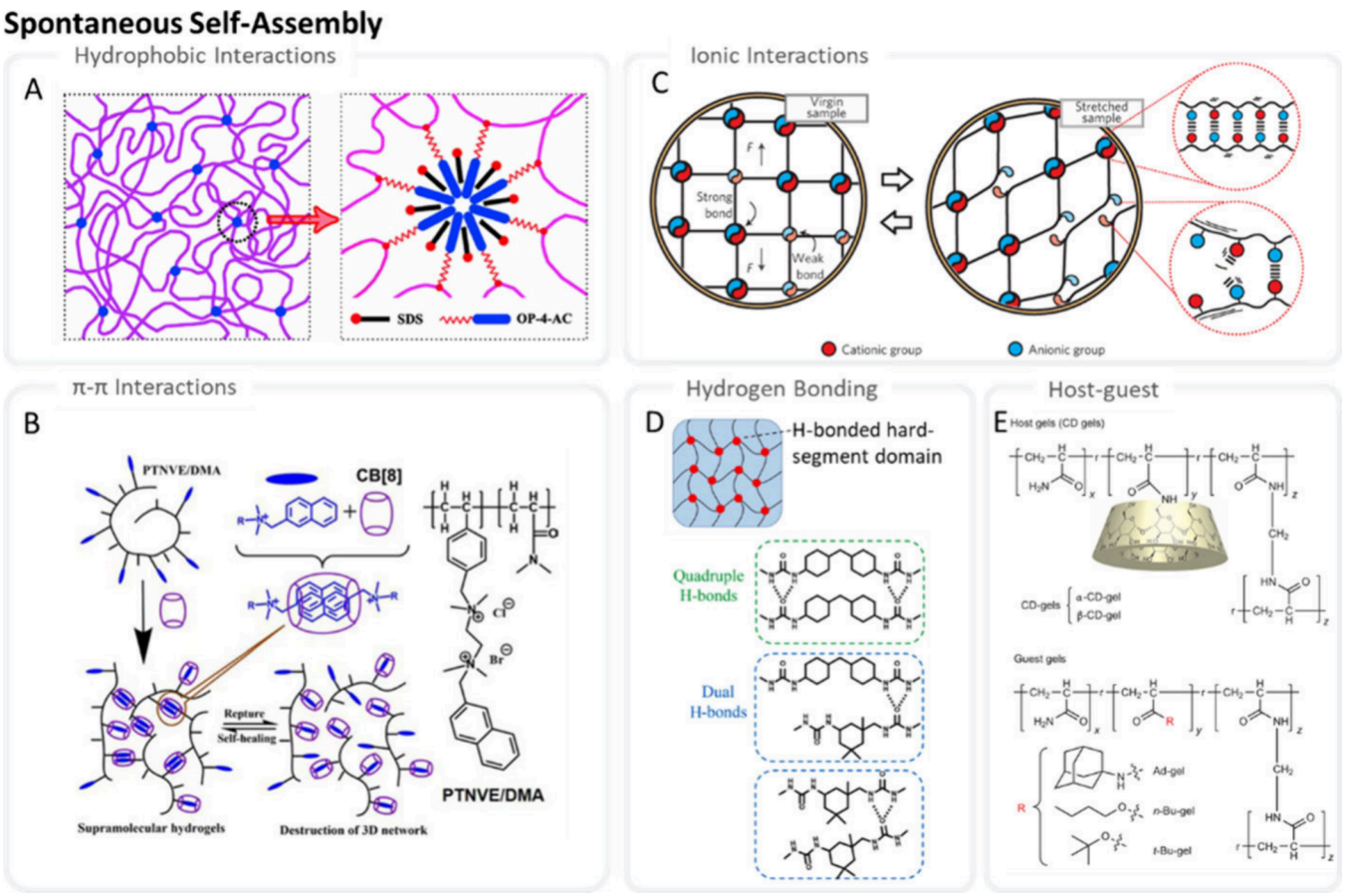

Figure 5. (A) The illustration of the structure of the associating networks within HA-gels. Reproduced with permission from ref. [170]. Copyright (2010) Elsevier. (B) Schematics of self-healing and formation of supramolecular hydrogels facilitated by CB[8]-enhanced π-π interaction among naphthalene groups within the side chains of copolymer PTNVE/DMA. Reproduced with permission from ref. [172]. Copyright (2016) Taylor & Francis. (C) Visual depiction of polyampholyte networks showcasing ionic bonds of varying strengths. Reproduced with permission from ref. [122]. Copyright (2013) Nature Publishing Group. (D) Molecular structure showing H-bonds of the PU hydrogel network. Reproduced with permission from ref. [171]. Copyright (2021) Elsevier. (E) Molecular structures of host and guest gels. Host gels include a-CD-gel and b-CD-gel, while guest gels encompass Ad-gel, *n*-Bu-gel, and *t*-Bu-gel. The character "r" in the polymer main chain denotes random copolymerization of each monomer. Reproduced with permission from ref. [173]. Copyright (2011) Nature Publishing Group.

rate as well as the morphology of aggregated structures.[148] Polymer aggregation processes are numerically described by two models: diffusion-limited cluster−cluster aggregation (DLCA) and reaction-limited cluster−cluster aggregation (RLCA). In a DLCA model, the probability of interchain interaction during each chain collision is close to unity, thus polymer chains will attach to the first chain they encounter, resulting in the formation of loosely connected, highly branched aggregates. The mass of these aggregates increases linearly with time, reflecting a steady aggregation process. Conversely, an RLCA model is defined by a much slower aggregation rate, where only a small percentage of collisions result in the bonding of polymer chains. Thus, polymer chains can diffuse and interpenetrate each other prior to aggregation, leading to the formation of denser structures. The mass of these aggregates grows exponentially over time, indicating a more complex aggregation process due to limited effective collisions.[149] The aggregated structures are frequently described in fractal dimensions, where the index number indicates the spatial occupation of polymer clusters as they grow — a lower fractal dimension indicates a more open, porous microstructure, while a higher fractal dimension corresponds to a more compact microstructure.[150] For instance, DLCA processes have a fractal dimension of around 1.7 to 1.8, while RLCA processes have a fractal dimension of approximately 2.0 to 2.2. The thermodynamic state of the system directly determines which kinetic aggregation pathway dominates.[151] When a system crosses into the unstable region through spinodal decomposition, the steep free energy gradients typically lead to DLCA behavior, as the high driving force for phase separation results in particles sticking upon first contact with near-unity probability. Conversely, in the metastable region where nucleation and growth dominate, RLCA mechanisms are more common because the smaller thermodynamic driving force results in a lower sticking probability during collisions. This difference in aggregation mechanisms is manifested in the resulting structures' fractal dimensions and growth kinetics - exponential growth with more compact structures (higher fractal dimension) in RLCA versus power-law growth with more open structures (lower fractal dimension) in DLCA. Harnessing the thermodynamic and kinetic principles, aggregation can progress favorably to form desired microstructures. Yet aggregation by noncovalent interactions is a reversible process, where dissociation occurs alongside aggregation. The rates of these two opposing processes can be influenced by factors such as temperature,[152]

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Chem. Rev. XXXX, XXX, XXX−XXX

pH,[153] and ionic strength.[154] Over time, a dynamic equilibrium is established where the rate of aggregation equals the rate of dissociation, finally resulting in a stable microstructure.[155]

The methods for inducing aggregation in hydrogels operate across multiple length scales, producing distinctly different structural outcomes that can be broadly categorized based on mechanism and resulting architecture. Molecular-level self-assembly produces ordered nanoscale microstructures through spontaneous directional interactions without external triggers,[156] while bulk phase separation methods (including cosolvent, nonsolvent, specific ion effects, ionization, ice templating, and annealing) create larger-scale polymer-rich and polymer-poor regions spanning microns to millimeters through spinodal decomposition or nucleation-and-growth mechanisms.[157] Other approaches include cross-linker-induced aggregation, which leverages multifunctional binding sites to create localized regions of polymer concentration; stimulus-triggered phase transitions that utilize external factors like temperature or light to induce conformational changes; and mechanical force-induced aggregation that employs physical stress to align and pack polymer chains.[158−160]

3.1. Spontaneous Self-Assembly

When the polymer−polymer interactions are stronger than the polymer−solvent interaction, polymer chains in hydrogels can aggregate without additional perturbation.[161] Such self-assembly can be driven by multiple types of interactions, including hydrophobic interactions,[162] hydrogen bonding,[163] electrostatic interactions,[164] π-π interactions,[165] stereo complex formation,[166] and host−guest interactions,[167] each contributing differently to the formation and properties of the resultant structures. Below, we examine how each major type of noncovalent interaction facilitates spontaneous aggregation in hydrogel systems. Self-assembly often occurs because the aggregated state minimizes the free energy of the system through these noncovalent interactions, and the corresponding kinetic barriers are low (i.e., self-assembly of small molecules and oligomers).[168] Although aggregation may decrease the entropy of the system, it can increase the entropy of the surrounding solvent, especially in hydrophobic interactions where water molecules are released from ordered hydration shells. These interactions allow the polymer chains to organize spontaneously into structured aggregates, enhancing the hydrogel's properties. This method is particularly effective for designing supramolecular hydrogels, which are formed from components that self-assemble through these noncovalent interactions. Such hydrogels are widely used in drug delivery systems due to their ability to form and degrade under physiological conditions without the need for chemical reactions.[169] While aggregation by self-assembly features simplicity during material processing, it can sometimes lead to less reproducible structures as minute variation in the processing conditions can divert the pathway of aggregation, potentially affecting consistency in applications. Here we discuss how hydrogels with aggregated structures are generated by each type of noncovalent interaction through self-assembly.

Hydrophobic Interactions: Jiang et al. explored the hydrophobic association hydrogels (HA-gels) synthesized through micellar copolymerization of acrylamide (AM) and a small amount of octylphenol polyoxyethylene acrylate (OP-4-AC, hydrophobic monomer) in the presence of sodium dodecyl sulfate (SDS, surfactant).[170] The self-assembly in HA-gels is illustrated in Figure 5A, which is induced by hydrophobic interactions between the octylphenol groups of hydrophobically modified PAAm and SDS, leading to the formation of hydrophobic domains that act as physical cross-linking points in the gel network. This process results in a structurally unique HA-gel, where the hydrophobic monomer OP-4-AC is distributed along the copolymer backbone, forming hydrophobic microblocks. The mechanical strength and the self-healing ability are contributed from aggregation within HA-gels. By varying the concentrations of OP-4-AC, SDS, and AM, the network structure, including the length of hydrophobic microblocks, the effective chain density, and the molecular weight between cross-linking points can be dynamically tuned. These parameters determine the mechanical behavior of HA-gels, including their tensile strength, fracture energy, elastic modulus, and elongation at break. Hydrophobic interactions drive the formation of micellar domains that act as physical cross-linking points, contributing to mechanical strength and self-healing properties. This form of self-assembly is particularly effective in systems containing amphiphilic components with well-defined hydrophobic segments.

Hydrogen Bonding: Wang et al. developed supramolecular polyurea (PU) hydrogels with a combination of hydrophilic soft segments and hard segments.[171] The hard segments contain aliphatic diisocyanates, which can form quadruple hydrogen bonds and dual hydrogen bonds, depending on the molar ratio of the diisocyanates as depicted in Figure 5D. The hard segments spontaneously aggregate into nanodomains induced by multiple hydrogen bonds. The aggregation provides the hydrogels with antiswelling properties and also contributes to tunable mechanical properties, including variations in elastic modulus, breaking strength, and elongation at break. The hydrogen bond network within the hydrogels can recover after deformation, allowing for self-recovery and resistance to mechanical hysteresis. Hydrogen bonding enables the formation of supramolecular networks through multiple bonding sites, creating nanodomains that contribute to mechanical robustness and antiswelling properties. This interaction is especially potent in polymers with abundant hydroxyl, carboxyl, or amide groups.

Ionic Interactions: Combining oppositely charged moieties may also result in aggregation and assembly of monomers and polymers. For example, Sun et al. presented a tough and viscoelastic polyampholyte hydrogel. This material is synthesized through the random copolymerization of an anionic monomer called sodium p-styrenesulfonate (NaSS), and a cationic monomer called 3-(methacryloylamino)propyl-trimethylammonium chloride (MPTC). The randomness in charge distribution within the polyampholytes leads to the formation of ionic bonds of varying strengths through inter- and intrachain complexation as shown in Figure 5C.[122] This structure results in a supramolecular hydrogel with both strong and weak ionic bonds. When the material is being stretched, the strong ionic bonds serve as the hydrogel's structural backbone, while the weak bonds allow for energy dissipation, contributing to the hydrogel's toughness, with a fracture energy of 4000 J/m^2 and self-healing capabilities, exhibiting 100% self-recovery. Ionic interactions between oppositely charged moieties create both strong and weak ionic bonds that contribute to structural integrity and energy dissipation mechanisms. This self-assembly approach is particularly valuable for developing tough, viscoelastic hydrogels with self-healing capabilities.

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π-π Interactions: When aromatic groups are installed on the polymer backbone, assembly may also be triggered via π-π interactions. A self-healing supramolecular hydrogel was developed by Cao et al., which was synthesized using a simple method that involves the preparation of a copolymer (poly(N^1,N^1,N^2,N^2-tetramethyl-N^1-(naphthalen-2-ylmethyl)-N^2-(4-vinylbenzyl)ethane-1,2-diaminium-*co*-N,N-dimethylacrylamide), PTNVE/DMA) followed by the addition of cucurbit[8]uril (CB[8]), which triggered the self-assembly by the π-π interactions between naphthalene units, leading to the formation of a stable ternary complex and ultimately resulting in the hydrogel's structure, as shown in Figure 5B.[172] These supramolecular hydrogels exhibit self-healing properties, a feature attributed to the reversible nature of the CB[8]-enhanced π-π interactions. The hydrogels' self-healing efficiency is also influenced by the CB[8] to naphthalene unit ratio, highlighting the tunability of their mechanical properties. π-π interactions between aromatic groups facilitate the formation of stable supramolecular complexes that exhibit self-healing properties. These interactions are especially useful in systems incorporating naphthalene, phenyl, or other aromatic moieties.

Host−Guest: Harada et al. demonstrates the macroscopic self-assembly of materials can be achieved through molecular recognition, specifically utilizing acrylamide-based gels functionalized with cyclodextrin (CD) hosts and hydrocarbon guest moieties.[173] The gels were synthesized through radical copolymerization that incorporates either cyclodextrin (as the host) or hydrocarbon groups (as the guest) into the polymer network. The host gels used were a-CD and b-CD gels, while the guest gels included adamantyl (Ad), *n*-butyl (*n*-Bu), and t-butyl (*t*-Bu) moieties, as depicted in Figure 5E. When host and guest gels come into contact, they adhere through molecular recognition between CDs and hydrocarbon groups on their surfaces. This adhesion is selective; for instance, b-CD gel binds strongly with Ad-gel via molecular recognition. This adhesion is strong enough that the assembled structures do not dissociate even at elevated temperatures. Host−guest interactions enable selective adhesion through molecular recognition, creating macroscopic assemblies with controllable properties. This mechanism is particularly powerful in cyclodextrin-functionalized systems that can recognize and bind specific guest molecules.

Stereoselective Interactions: Stereoselective interactions drive spontaneous self-assembly when molecular chirality dictates the preferential aggregation of polymer chains. A notable example is DNA hydrogels, where the Watson−Crick base-pairing mechanism enforces a highly specific and directional self-assembly process. The chiral nature of nucleotides enables precise molecular recognition, leading to the formation of stable double-helical structures that further aggregate into entangled polymeric networks.[47] This self-assembly is thermodynamically favorable, as it minimizes system free energy through a combination of hydrogen bonding and π-π stacking between stacked nucleobases. The resulting hydrogel exhibits tunable viscoelasticity, making it highly applicable in bioelectronics, controlled drug release, and molecular sensing.[128] Stereoselective interactions drive highly specific self-assembly based on molecular chirality, forming stable structures through complementary binding. This mechanism is exemplified in DNA hydrogels where precise base-pairing creates complex and well-defined architectures.

3.1.1. Operational Windows and Precautions.

The success of spontaneous self-assembly hinges primarily on polymer concentration and other environmental conditions that influence molecular mobility. The spontaneous self-assembly of MAX1 peptide into hydrogels is highly concentration-dependent. At concentrations below 1 wt %, peptides may fold into β-hairpins but self-assembly is slow and incomplete, taking several hours and failing to form a robust gel. In contrast, concentrations at or above 1 wt % enable rapid self-assembly and formation of stable hydrogels within minutes. Higher concentrations (e.g., 2 wt %) further enhancing gel strength and assembly speed.[174] The assembly process is also highly sensitive to temperature, pH, and ionic strength, with optimal conditions typically occurring near the pK_a of functional groups for pH-dependent systems. The key precaution is to avoid rapid environmental changes that can trap the system in metastable states rather than allowing it to reach thermodynamic equilibrium, resulting in heterogeneous or poorly defined structures.

3.2. Perturbation of Solvation

While spontaneous self-assembly leverages inherent polymer−polymer attractions, solvation perturbation methods actively alter the balance between polymer−solvent and polymer−polymer interactions to induce aggregation.[175−177] These techniques are particularly effective at enhancing hydrogen bonding and hydrophobic interactions by reducing the solvent quality or altering the solvation environment. The following subsections explore different approaches to solvation perturbation and highlight which noncovalent interactions are most significantly affected by each method.

3.2.1. Cosolvent.

A unique case of dissolving polymers with cosolvents occurs when two good solvents are mixed at a certain ratio and transform into poor solvents, leading to polymer phase separation. This phenomenon is known as cononsolvency, which involves a complex interplay of hydrogen bonding and hydrophobic interaction that affect the solubility of the polymer in the mixed solvent system.[178] Thermodynamically, when such a cosolvent is added, the interaction parameter between polymer and solvent increases, creating a second local free energy minimum on the curve.[179] The system minimizes free energy by reducing unfavorable polymer−solvent interactions and enhancing favorable polymer−polymer interactions, leading to phase separation aggregation. Kinetically, the competition between phase separation and noncovalent cross-links formation is dependent on temperature, viscosity, etc., which ultimately determines when the phase separation process become fixed in space by physical cross-linking.[180] Using cosolvents to induce aggregation allows for fine-tuning of hydrogel properties, such as mechanical and antifreezing behaviors,[181] by varying the composition of the cosolvent mixture. In addition, the phase separation process enables formation of unique porous structures, which are beneficial for applications that rely on transport of matter through the hydrogel matrix.[182] However, the number of practical cononsolvent systems is limited, and the exploration of new systems would require careful optimization and testing.

Hydrogen Bonding: Cononsolvency systems can elicit aggregation through promoting hydrogen bond formation. Wu et al. developed antifreezing conductive gels using PVA through a water/dimethyl sulfoxide (DMSO) binary liquid system. This system acts both as a gelation inducer via the

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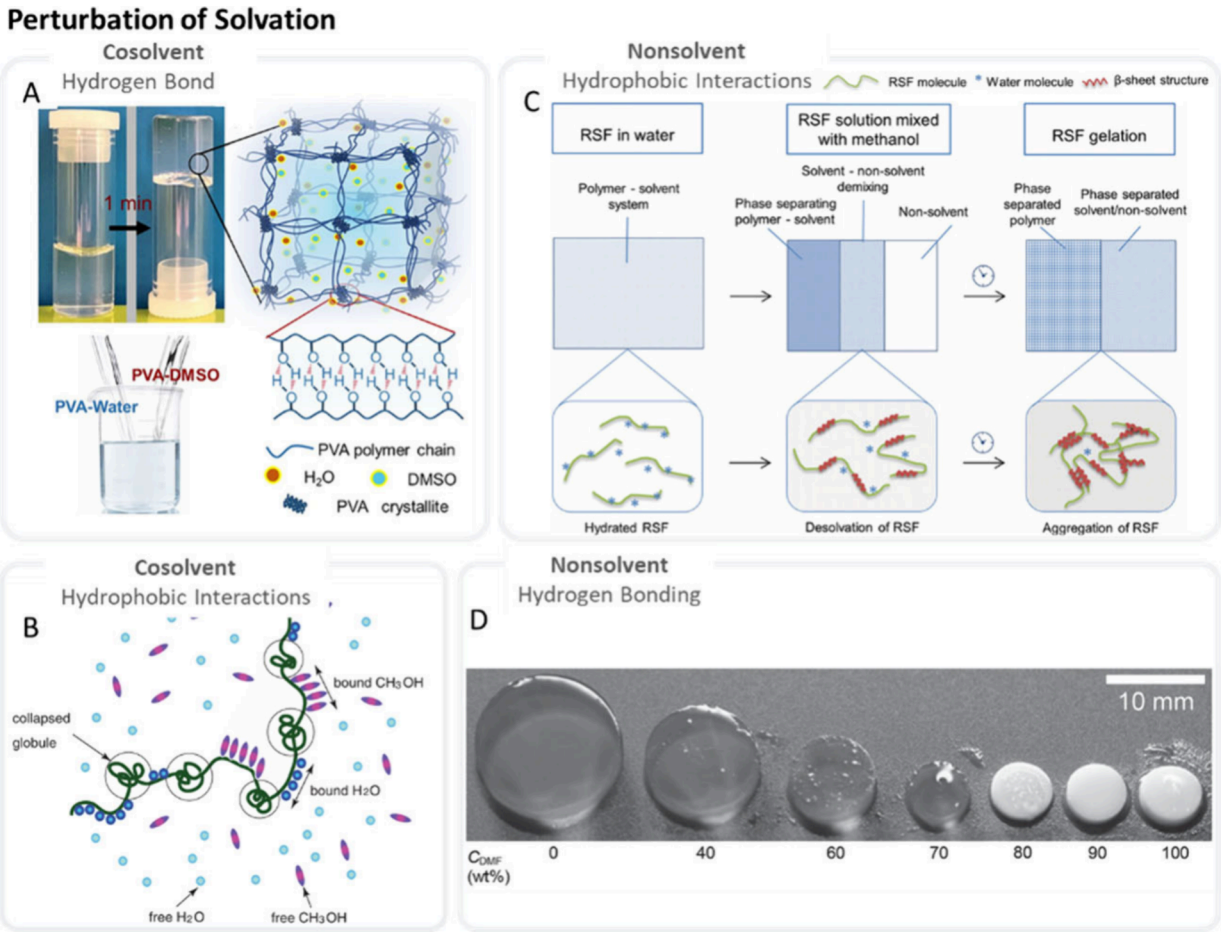

Figure 6. (A) Gelation mechanism of antifreezing gels initiated by the cononsolvency effect. Reproduced with permission from ref. [31]. Copyright (2021) Wiley. (B) Interplay between PNIPAM-water and PNIPAM-methanol hydrogen bonding. Reproduced with permission from ref. [183]. Copyright (2008) American Physical Society. (C) Mechanistic insight into RSF hydrogels formation via nonsolvent induced phase separation. Reproduced with permission from ref. [189]. Copyright (2016) Royal Society of Chemistry. (D) Visualization and volumetric changes of PAAm hydrogels in DMF/water solvent. Reproduced with permission from ref. [188]. Copyright (2015) Wiley.

cononsolvency effect and as antifreezing solvents.[31] As illustrated in Figure 6A, the gels are prepared by mixing aqueous solutions of PVA with DMSO solutions of PVA at varying ratios. The optimal composition found was 60 wt % DMSO, which facilitates rapid gelation within minutes at −20 °C. The aggregation process within the gels occurs due to the cononsolvency effect, where water and DMSO preferentially interact with each other over PVA, leading to the phase separation of PVA chains and the formation of inter- and intrachain hydrogen bonds. These hydrogen bonds act as physical cross-linkers, resulting in gelation. At subzero temperatures the gelation rate is increased and the resulting material is transparent and stretchable. The gels demonstrate superior mechanical properties, including a tensile strength of 1.1 MPa, toughness of 10.9 MJ/m^3, and elongation at break of 1500%, surpassing most existing hydrogels.

Hydrophobic Interactions: In hydrogels that do not contain significant densities of polar functional groups, hydrophobic interactions may substitute hydrogen bonding for inducing aggregation in a cononsolvency system. Tanaka et al. investigated the behavior of PNIPAM in the mixture of water and methanol.[183] The schematic of such a system is illustrated in Figure 6B. PNIPAM has temperature-responsive behavior in water, showing a sharp transition from a swollen (coil) to a collapsed (globule) state at around 34.5 °C, known as the lower critical solution temperature (LCST). The addition of a second solvent like methanol to water causes PNIPAM to undergo a coil-to-globule transition at certain mixed solvent compositions. The cononsolvency effect and the polymer's aggregation behavior are attributed to competitive hydrogen bonding between the polymer chain and solvent molecules. In pure solvents, PNIPAM is well-hydrated by water due to hydrogen bonding. However, when methanol is introduced, it competes with water for hydrogen bonding sites on the PNIPAM chain. This competition, coupled with the cooperativity in hydration (positive correlation between neighboring bound water molecules) and hydrophobic interaction between the isopropyl functional groups, leads to significant changes in the polymer's conformation. The model suggests that there are less amount of hydrogen bonds along the PNIPAM chain in a mixed solvent, resulting in collapsed chain at specific methanol compositions.

The cononsolvency method primarily exploits two major types of noncovalent interactions to drive polymer aggregation. Hydrogen bonding plays a central role as demonstrated in PVA systems with water/DMSO mixtures, where the competitive interactions between solvents promote enhanced interchain hydrogen bonding. Simultaneously, hydrophobic interactions are significantly strengthened, particularly in systems like PNIPAM, where cononsolvency enhances hydrophobic

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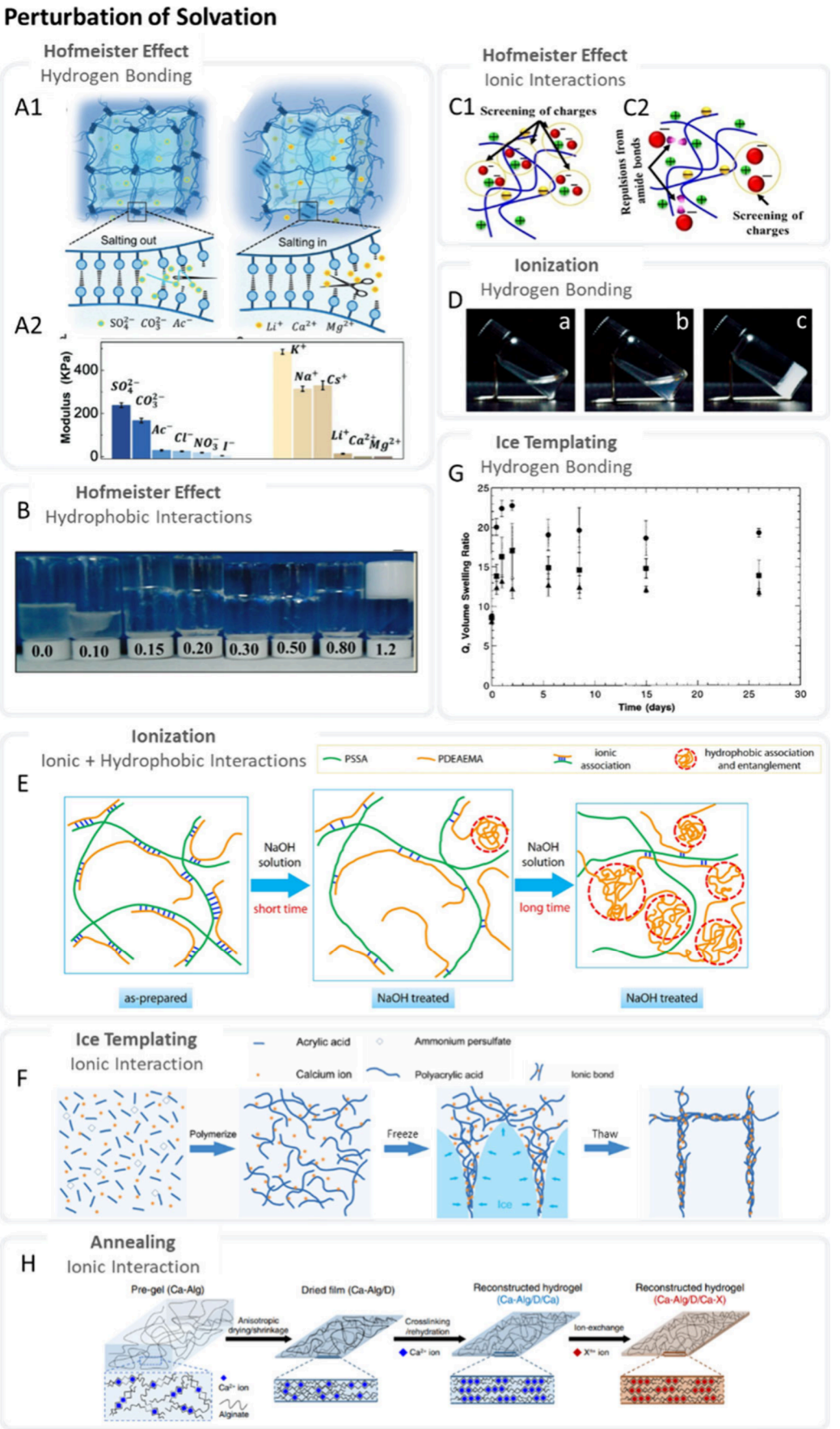

Figure 7. (A1) Aggregation of PVA polymer chains soaked in different ion solutions. (A2) Moduli variations of PVA hydrogels influenced by diverse anions (with Na^+ as the constant counterion) and various cations (with Cl^- as the constant counterion). Reproduced with permission from

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Chem. Rev. XXXX, XXX, XXX−XXX

Figure 7. continued

ref. [193]. Copyright (2021) Wiley. (B) Photographs of solutions in inverted glass vials after 1 day of reaction, with salt concentrations denoted in M. Reproduced with permission from ref. [194]. Copyright (2011) American Chemical Society. (C1) Schematic representation detailing interactions between chaotropes and gelatin. (C2) Schematic illustration of interactions between kosmotropic ions and gelatin. Reproduced with permission from ref. [195]. Copyright (2024) Wiley. (D) C_{12}-GAGAGAGY/H_2O system at different pH conditions: (a) pH 11, (b) pH 8, and (c) around pH 4. Reproduced with permission from ref. [206]. Copyright (2013) American Chemical Society. (E) Schematic representation of the network structure for both as-prepared and NaOH-immersion-treated hydrogel. Reproduced with permission from ref. [207]. Copyright (2024) American Chemical Society. (F) Methodology for preparing the freeze−thawed Ca^{2+}/PAAc hydrogel. Reproduced with permission from ref. [213]. Copyright (2020) Springer. (G) Initial swelling in water at 37 °C of PVA samples subjected to three (circle), five (square), and seven (triangle) cycles of 8 h freezing and 4 h thawing. Reproduced with permission from ref. [214]. Copyright (2000) American Chemical Society. (H) Schematics of the fabrication of the alginate hydrogel by anisotropic drying/shrinkage and cross-linking/rehydration. Reproduced with permission from ref. [219]. Copyright (2022) Nature Publishing Group.

aggregation through competitive solvation and dehydration effects. The interplay between these interactions creates uniquely structured hydrogel networks that combine mechanical robustness with responsive properties.

3.2.2. Nonsolvent. A polymer, initially dissolved in a solvent, can be induced to phase separate into a polymer-rich phase and a polymer-poor phase by the introduction of a nonsolvent.[184] In such systems, the nonsolvent is miscible with the solvent but does not dissolve the polymer. The introduction of a nonsolvent alters the chemical potential of the polymer chains, often resulting in a decrease in the free energy of the system when the polymer aggregates driven by a favorable change in enthalpy or entropy upon aggregation.[185] Like the cosolvent induced aggregation, the kinetics of polymer chain diffusion and physical interaction formation also dictate the morphology of the aggregated material. Nonsolvent-induced phase separation offers a straightforward method to create highly structured hydrogels with enhanced mechanical properties and self-healing capabilities.[186] However, this method can result in phase separation that is difficult to control, particularly due to the rate of aggregation is often significantly higher than the rate of diffusion for homogeneous mixing of the solvents, potentially leading to heterogeneity in the material's properties.[187]

Hydrogen Bonding: Sato et al. reported PAAm gels that undergo nonsolvent induced phase separation by hydrogen bonding formation.[188] Acrylamide (AAm) and N,N'-methylenebis(acrylamide) (MBAA) are polymerized to synthesize the PAAm gels. The resultant gels were then immersed in mixtures of N,N-dimethylformamide (DMF)/water, which are poor/good solvents for PAAm, respectively, inducing phase separation. Figure 6D shows that the addition of DMF in the samples induced significant aggregation, causing volume shrinkage and transparency change. The immersion in DMF/water mixtures led to phase separation within the gels, characterized by the formation of dense polymer domains due to reduced solvent quality. The phase-separated gels exhibited remarkable mechanical properties. They showed a significant increase in stiffness and toughness when the concentration of DMF reached a critical level, undergoing a gel-to-glass-like transition. These gels displayed very high fracture energy and stiffness; orders of magnitude higher than those without phase separation. Notably, the phase separation induced a unique self-healing capability in the gels, allowing them to recover their original mechanical properties after damage.

Hydrophobic Interactions: Hydrophobic interactions are equally effective for inducing aggregation in the presence of a nonsolvent. Kasoju et al. investigated the process of creating *Bombyx mori* silk fibroin hydrogels using nonsolvent induced phase separation (NIPS).[189] The gels were fabricated by mixing aqueous reconstituted silk fibroin (RSF) solutions with methanol at various concentrations, followed by incubation at different temperatures. The mechanism of RSF hydrogel formation by nonsolvent induced phase separation is shown in Figure 6C. In water, RSF molecules are stabilized by reduced molecular friction, allowing for more conformational flexibility. However, adding methanol disrupts this by engaging in proton exchange with water, which impairs its interaction with RSF. Consequently, RSF precipitates, and its inherently hydrophobic and block copolymer characteristics drive conformational changes, leading to phase separation and forming a highly ordered crystalline structure. The formation of RSF hydrogels through NIPS significantly impacts their mechanical and chemical properties. The gels exhibit increased stiffness, toughness, and self-healing abilities, with the degree of these properties being tunable by adjusting the methanol content, RSF concentration, and incubation conditions.

The nonsolvent approach harnesses specific noncovalent interactions to create structurally unique hydrogels. Hydrogen bonding is significantly enhanced through this method, as evidenced in PAAm systems with DMF/water mixtures, where the presence of the nonsolvent forces polymer chains into closer proximity, strengthening interchain hydrogen bonds and creating robust physical cross-links. Concurrently, hydrophobic interactions are amplified in systems like silk fibroin, where nonsolvent addition promotes hydrophobic domain formation by reducing the solubility of hydrophobic segments, leading to their aggregation and the formation of stabilizing hydrophobic junctions. These combined effects result in hydrogels with enhanced mechanical properties and controlled phase separation characteristics.

3.2.3. Specific Ion Effect. Instead of tuning solvents, the aggregation of polymers can also be governed by addition of specific solutes. One effective strategy in this category is closely related to specific ion effect.[190] This phenomenon refers to the influence of different salt ions on polymer solubility in aqueous solutions, which originate from the polarization of hydration water, the increase of the surface tension of the cavity surrounding the nonpolar surfaces of the polymer, as well as the direct binding of ions to specific moieties on the polymer.[191] Based on the overall outcome of these effects, ions can be categorized into Kosmotrops and chaotropes.[192] Kosmotropic ions can enhance polymer aggregation by stabilizing water structure and reducing solvation shell, making polymer−polymer interactions more favorable (Salting-out). While chaotropic ions can enhance solubility and stabilize the polymer chains (Salting-in). The addition of salt can change the chemical potential of the polymer, thereby shifting the

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Chem. Rev. XXXX, XXX, XXX−XXX

balance between polymer−solvent and polymer−polymer interactions. When utilizing the specific ion effect to induce polymer aggregation, the diffusion rate of polymer chains and the rate of salt addition can both influence the rate of aggregation and result in aggregated structure.

Hydrogen Bonding: One well demonstrated example of applying Hofmeister effect for modulating aggregated polymer structures is based on promoting hydrogen bond formation in polymers. Wu et al. introduced a novel approach for significantly altering the mechanical properties of PVA hydrogels through the Hofmeister effect.[193] A solution of PVA is first frozen, then soaked in different salt solutions. This process allows PVA to interact with ions and aggregate. This method enables systematic adjustment of hydrogel properties by changing the type and concentration of ions in the soaking solution, as specific ions influence the hydration water around hydrophilic functional groups on polymer chains, leading to varying strength of salting-out or salting-in of polymers. As shown in Figure 7A1, salting-out ions, like sulfate, promote the aggregation and crystallization of polymer chains by destabilizing the hydrogen bonds with water. In contrast, salting-in ions, such as iodide, increase polymer solubility and reduce aggregation. The comparison of the strengths of salting-out is plotted in Figure 7A2, which shows the moduli of salt-treated samples with various anions (with Na^+ as the constant counterion) and different cations (with Cl^- as the constant counterion). PVA hydrogels interacted with various ions exhibited a wide range of mechanical properties. The study shows hydrogels with tensile strengths ranging from 50 ± 9 kPa to 15 ± 1 MPa, toughness from 0.0167 ± 0.003 to 150 ± 20 MJ m^{-3}, elongation from 300 ± 100% to 2100 ± 300%, and modulus from 24 ± 2 to 2500 ± 140 kPa.

Hydrophobic Interactions: Hydrophobic functional groups on polymers are also affected by Hofmeister effects. Tuncaboylu et al. explored the synthesis of unique self-healing hydrogels through the copolymerization of hydrophobic monomers (stearyl methacrylate (C18) and dococyl acrylate (C22)) with a hydrophilic monomer (acrylamide).[194] The fabrication process involves the micellar copolymerization technique, where hydrophobic monomers are solubilized within SDS micelles and copolymerized with acrylamide in aqueous solutions. The hydrophobic interactions between blocks of C18 or C22 units within the hydrogel network are essential for its formation. These interactions are induced by the presence of NaCl, which facilitates the growth of SDS micelles and the solubilization of hydrophobic monomers. Figure 7B displays photos of reaction solutions in inverted vials after 1 day. Without NaCl, a turbid polymer solution was formed due to the hydrophobic comonomer's instability in SDS solution. Gel formation commences above 0.1 M NaCl, accompanied by decreasing turbidity with increasing salt concentration. Transparent gels are achieved within the 0.3 to 0.8 M salt concentration range, facilitated by complete solubilization of C18 in SDS micelles. However, higher salt contents lead to phase separation during polymerization, resulting in opaque gels or solutions, indicating micelle aggregation. The resulting hydrophobic associations act as physical cross-links, preventing the hydrogel from dissolving in water and contributing to its self-healing capabilities. The hydrogels exhibit remarkable self-healing efficiency, with the ability to recover their original mechanical properties after being fractured. This is attributed to the dynamic nature of the junction zones within the gel network, where hydrophobic blocks can disengage and reassociate to heal the material. Additionally, the hydrogels demonstrate high toughness and flexibility, with the ability to withstand extensive stretching.

Ionic Interactions: Hofmeister effect can be further paired with polyelectrolyte hydrogels to induce aggregation via disruption of ionic interactions. Das et al. developed cross-linker-free gelatin-alginate hydrogels and their modification through the Hofmeister effect.[195] The study uses two types of salts: kosmotropes (e.g., Na_2SO_4, CH_3COONa), which promote the salting out of proteins, and chaotropes (e.g., NaCl, $NaNO_3$), which result in salting in. These salts, along with plasticizers like PEG and glycerol, are mixed with gelatin (gelatin) and alginate to form the hydrogels, aiming for improved design flexibility in biomaterials. The study suggests that the ions modify the electrostatic interactions between polymer chains, affecting the formation of hydrogen bonds and, subsequently, the hydrogel's properties. As shown in Figure 7C1 and C2, Kosmotropes generally result in better drug release profiles, higher gel strength, and more rapid degradation, making them suitable for applications requiring controlled drug delivery. In contrast, chaotropes enhance the hydrogels' self-healing capabilities by promoting hydrogen bonding.

The specific ion effect represents a versatile approach that engages multiple noncovalent interactions simultaneously. Hydrogen bonding is profoundly influenced by kosmotropic ions, which enhance interchain hydrogen bonds by destabilizing polymer−water interactions, as clearly demonstrated in PVA hydrogels where salt treatment leads to dramatic mechanical property enhancement. Hydrophobic interactions are equally affected, with salt-induced micelle growth promoting hydrophobic associations in systems containing amphiphilic components, creating physically cross-linked domains that contribute to structural integrity. Additionally, ionic interactions play a direct role as specific ions modulate electrostatic attractions between polymer chains, significantly affecting gel strength, toughness, and degradation properties. This multifaceted influence on various noncovalent interactions makes the specific ion effect a particularly powerful tool for precisely tuning hydrogel properties across different application requirements.

3.2.4. Ionization. Aggregation in hydrogels can also be induced by changing the pH. For instance, ionized carboxylic acid groups protonate at low pH,[196] while ionized amines deprotonate at increased pH.[197] The solubility of polymer chains,[198] electrostatic interaction between chains,[199] hydrogen bonding[200] can also be altered alongside the change in ionization. In general, when the degree of ionization is reduced, polymer−polymer interactions become more favorable compared to polymer−solvent interactions, promoting the formation of aggregated state.[201] From the kinetics perspective, the rate of pH change,[202] electrostatic attraction and repulsion,[203] as well as the hydrodynamic radius[204] can affect the probability of interchain interaction and the rate of chain diffusion, determining the morphology. Such pH responsive hydrogels are highly useful for applications where environmental pH changes can trigger a response, such as targeted drug delivery in tumor tissues. However, unintentional pH fluctuations in the environment will similarly alter the hydrogel's properties, affecting its performance and reliability, especially when serving as structural materials.[205]

Hydrogen Bonding: Guo et al. developed a robust hydrogel using a peptide amphiphile (PA) derived from silk fibroin.[206]

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Chem. Rev. XXXX, XXX, XXX−XXX

The hydrogels are formed by dissolving C_{12}-GAGAGAGY in a sodium hydroxide solution. pH is adjusted to desired levels using hydrochloric acid, which allows the polymer chains to form hydrogen bonds and induces gelation. At higher pH values, the peptide amphiphiles form cylindrical nanofibers. As the pH decreases, tyrosine residues on the peptide lead to the formation of nanoribbons that aggregate into parallel bundles due to the neutralization of carboxyl groups and the reduction of electrostatic repulsion, resulting in the formation of a structured hydrogel, which is shown in Figure 7D. The hierarchical aggregation of C_{12}-GAGAGAGY results in a hydrogel with remarkable mechanical strength (modulus around 10^5 Pa) and plasticity. The hydrogel exhibits a reversible sol−gel transition, responsiveness to pH changes, and the ability to self-heal, making it suitable for applications requiring robust and adaptable materials.

Ionic + Hydrophobic Interactions: Zhang et al. explored the dynamic mechanical behavior of polyion complex hydrogels that incorporate monomers with hydrophobic groups.[207] The hydrogels are synthesized through homopolymerization of the cationic monomer in the presence of the polyanionic poly(4-styrenesulfonic acid) (PSSA) aqueous solution, as depicted in Figure 7E. Upon exposure to NaOH, the ionic bonds between PSSA and the cationic polymer chains weaken, reducing the ionic interactions between polymer chains. After a longer soaking period, this initial softening will be followed by the formation of hydrophobic associations among cationic polymer chains, which will lead to an increase in the modulus and work of extension of the hydrogel. This pH-induced mechanical transition enables the hydrogel to exhibit unique properties, including significant elongation, high modulus, and toughness without substantial water uptake or release.

Ionization-induced aggregation in hydrogels operates through a sophisticated interplay of different noncovalent interactions. Hydrogen bonding behavior undergoes significant transformation as pH changes alter the protonation state of functional groups like carboxylic acids and amines, directly influencing their hydrogen bonding capabilities and strengths. Simultaneously, ionic interactions are precisely modulated in pH-responsive systems, where changing pH values can enhance or diminish electrostatic attractions between oppositely charged segments, creating dynamic cross-linking that responds to environmental conditions. Furthermore, hydrophobic interactions are affected as protonation or deprotonation events can fundamentally shift the hydrophilic−hydrophobic balance of polymer chains, triggering conformational changes and subsequent aggregation. This intricate orchestration of multiple interaction types through simple pH adjustments makes ionization a particularly elegant and versatile approach for creating responsive hydrogel systems.

3.2.5. Ice Templating. An alternative but efficient way to perturb solvation for creating aggregated structures is to crossover the phase boundaries and inhibit solvation of polymers through crystallization of the solvent. Ice templating is often employed as the main solvent in hydrogels is water.[208] This technique involves freezing a polymer solution to create ice crystals, which condenses the polymer solution to regions between the ice crystals. As the ice melts, it leaves behind a porous structure, with the polymer chains aggregated around the ice crystal templates. The local polymer concentration in regions between ice crystals is higher than in the precursor solution, promoting aggregation due to entropic gains from solvent exclusion and enthalpic contributions from polymer−polymer interactions. The size, shape, and orientation of ice crystals formed during freezing are governed by both the thermodynamics and kinetics aspects of the system, including factors such as the rate of cooling, the concentration of solutes, and the intrinsic properties of the solution.[209] This technique is particularly useful for creating scaffolds in tissue engineering,[210] where the porous structure can support cell infiltration[211] and tissue growth.[212] This method is relatively straightforward and does not require complex chemicals. However, the process can be time-consuming and may introduce variability in the pore structure depending on the specific instrument setup, affecting consistency in material properties.

Ionic Interactions: Cao et al. developed a highly stretchable hydrogel composed of calcium ions and PAA utilizing a freezing-thawing method.[213] The hydrogel is initially formed by polymerizing acrylic acid in a calcium chloride solution, creating a soft and weak gel. This initial hydrogel undergoes a subsequent cyclic freezing-thawing process illustrated in Figure 7F. During the freezing phase, ice crystals concentrate polymer and calcium ions, leading to enhanced ionic bonding between calcium ions and the carboxylate groups of the PAA chains. When the ice melts during the thawing phase, these enhanced ionic bonds remain intact, resulting in a hydrogel with a more tightly cross-linked network. The freeze−thaw process significantly strengthens the hydrogel, allowing it to endure strains up to 1100% and fracture at a stress of 0.6 MPa. The hydrogel also exhibits low hysteresis (less than 5% at 200% strain) and good recovery up to 800% strain. These properties are attributed to the increased density of ionic bonds formed during the freezing phase.

Hydrogen Bonding: Hassan et al. investigates the properties of PVA hydrogels formed through a freeze/thaw process.[214] The hydrogels are fabricated by dissolving PVA in water and then casting the solution into molds, followed by a series of freeze/thaw cycles. During the freezing phase, ice crystals form and grow within the PVA solution, excluding the PVA molecules and pushing them together into concentrated areas, which promotes hydrogen bonding and crystallization among PVA chains. Upon thawing, the ice melts, leaving behind a network of physically cross-linked PVA. Figure 7G plots the swelling ratios of samples with three, five, and seven cycles of 8 h freezing and 4 h thawing, which indicates repeated freeze/thaw cycles can increase the density of these cross-links, leading to stronger and more stable hydrogels. These gels exhibit high mechanical strength and elasticity, important for applications such as artificial tissues and contact lenses.

Ice templating strategically leverages specific noncovalent interactions to create uniquely structured hydrogels. Hydrogen bonding is substantially enhanced during this process as freezing concentrates polymer chains into the interstitial spaces between growing ice crystals, significantly promoting interchain hydrogen bond formation, as elegantly demonstrated in PVA systems where freeze−thaw cycles progressively strengthen the hydrogen-bonded network. Complementing this effect, ionic interactions are intensified as ice crystal growth concentrates ionic species into confined regions, dramatically enhancing ionic cross-linking density and strength, as evidenced in calcium-PAA hydrogels where freezing creates highly cross-linked ionic domains with superior mechanical properties. The combined influence on these interactions, coupled with the structural templating effect of ice crystals,

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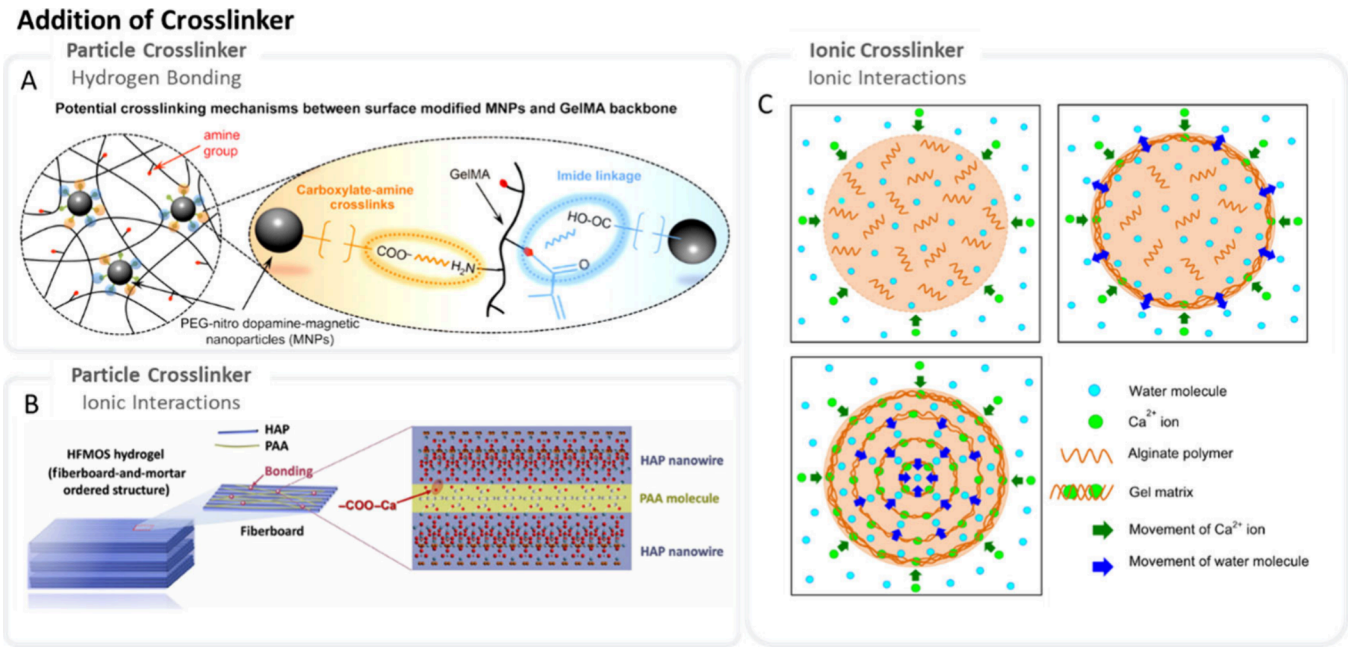

Figure 8. (A) Proposed mechanism for cross-linking between surface-modified MNPs and the gelatin methacryloyl (GelMA) polymer backbone. Reproduced with permission from ref. [238]. Copyright (2016) American Chemical Society. (B) Schematic representation of the flexible, high-strength, and versatile HFMOS hydrogel composed of highly ordered ultralong HAP nanowires and PAA serving as the glue. This material exhibits a hierarchically ordered structure resembling fiberboard-and-mortar. Reproduced with permission from ref. [239]. Copyright (2021) Springer. (C) Proposed mechanism elucidating the multilayer formation of calcium-alginate matrices within 10% w/v calcium alginate beads. Reproduced with permission from ref. [225]. Copyright (2016) Elsevier.

enables the creation of hierarchically porous hydrogels with exceptional mechanical and transport properties difficult to achieve through other methods.

3.2.6. Annealing. Annealing of hydrogels involves heating and subsequent cooling processes.[215] Similar to ice templating method, the removal of solvent increases the polymer concentration, promoting noncovalent interactions and aggregation of polymer chains. This leads to rearrangement and reorganization within the hydrogel matrix, enhancing its structural integrity through mechanisms such as hydrogen bonding,[216] ionic interactions,[217] and van der Waals forces.[218]

Ionic Interactions: Ji et al. present a method to fabricate superstrong, superstiff, and conductive alginate hydrogels.[219] The materials used include alginate (Alg), calcium sulfate, and various ionic cross-linking agents (Figure 7H). The fabrication process involves anisotropic drying and shrinkage of a pregel, followed by rehydration and ionic cross-linking. Interconnected and dense polymer networks with enhanced mechanical properties were formed by this reconstruction method. Depending on the ions used, the tensile strength ranges from 8 to 57 MPa, and the elastic modulus varies from 94 to 1290 MPa. Additionally, incorporating conducting polymers like PEDOT into the hydrogel matrix provides high ionic and electrical conductivity. These properties enable the hydrogel to be used as a solid gel electrolyte in applications such as aqueous supercapacitors, demonstrating potential for robust and conductive hydrogel materials.

Annealing processes in hydrogel fabrication selectively enhance specific noncovalent interactions to optimize structural and mechanical properties. Ionic interactions are particularly influenced by annealing treatments, which significantly enhance ionic network formation in systems like alginate hydrogels with multivalent cations, creating more uniform and robust ionically cross-linked domains. Concurrently, hydrogen bonding networks undergo substantial reorganization during thermal treatment, as elevated temperatures provide sufficient energy for hydrogen bonds to break and reform in more thermodynamically favorable configurations, resulting in more perfectly aligned and stronger interchain connections. This thermal reorganization of noncovalent interactions through annealing represents a powerful approach for enhancing hydrogel performance without introducing additional chemical components, making it particularly valuable for applications with stringent purity requirements.

3.2.7. Operational Windows and Precautions. The efficacy of solvent perturbation methods varies across specific techniques. PVA hydrogels prepared via cononsolvency are extraordinarily sensitive to solvent composition, with the optimal mechanical properties occur only within the narrow 55−65 vol % DMSO range, outside of which dramatic weakening occurs.[31] For polysaccharide-based hydrogel systems undergoing ice-templated freeze-drying, using a low cooling rate of 0.1 °C/min produces uniform and equiaxed pore structures. In this condition, the ice nucleation temperature varies between − 6 °C and − 18 °C, with controlled supercooling of 6−18 °C directly influencing pore size. A lower nucleation temperature (higher supercooling) leads to smaller ice grains and smaller final pore sizes, while higher nucleation temperatures result in larger pores. Cooling rates above 1 °C/min or uncontrolled nucleation can cause heterogeneous or columnar solidification, reducing the uniformity of the porous structure.[220] Across all these methods, the universal precaution is to ensure homogeneous distribution of the perturbation stimulus throughout the polymer solution to prevent localized aggregation that leads to structural heterogeneity.

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Chem. Rev. XXXX, XXX, XXX−XXX

3.3. Addition of Cross-linker

While the methods described above primarily alter polymer−solvent interactions, cross-linker addition directly enhances polymer−polymer interactions by introducing binding agents that bridge multiple polymer chains.[221,222] These methods are particularly effective at leveraging ionic interactions and hydrogen bonding to create physically cross-linked networks with enhanced mechanical properties. The following subsections explore different cross-linking approaches and identify which noncovalent interactions are predominantly activated in each case.

3.3.1. Ionic Cross-linker. The addition of ion is a versatile method to control hydrogel properties, such as enhancing mechanical strength or inducing specific aggregation patterns. Electrostatic attraction between the charged ions and the functional groups on polymer carrying opposite charge serves as the primary driving force for binding, which significantly lowers the system's electrostatic potential energy.[223] The aggregate structure can be controlled by factors such as the rate of ion addition, the competition with other ions and polymer chain diffusion. This method allows for fine control over the material's properties by varying the type and concentration of ions, yet the presence of certain metal ions can sometimes introduce issues with long-term stability or biocompatibility, particularly in biological applications.[224]

Ionic Interactions: Voo et al. presents a method for creating calcium alginate beads that exhibit enhanced mechanical strength and prolonged dissolution times.[225] The fabrication process involves a novel approach using a temperature-controlled extrusion system with an interphase column containing oil (top layer) and calcium chloride solution (bottom layer). This setup allows for the formation of spherical beads directly from an alginate solution. The process is illustrated in Figure 8C. Initially, high concentrations of alginate precursor facilitate the formation of a dense cross-linked layer on the peripheral of the alginate droplet. Subsequently, water expulsion from the cross-linked shell into the inner core region creates a water-rich layer between the cross-linked shell layer and the non-cross-linked core layer. Continuous inward diffusion of Ca^{2+} ions repeatedly trigger the cross-linking of new layers of alginate, progressively creating new cross-linked layers toward the droplet center. Concentric spheres form from aggregation through ionic interactions. The ultrahigh concentration calcium alginate beads exhibit a Young's modulus value of 3.6 MPa, approximately eight times higher than that of normal calcium alginate beads. Furthermore, the drug release profile for methylene blue encapsulated in the beads extends to 4 h at 80% drug release.

The ionic cross-linker approach predominantly exploits electrostatic interactions to create physically cross-linked hydrogel networks with tailored properties. Multivalent cations serve as versatile bridging agents, forming electrostatic connections between negatively charged polymer segments through coordinated ionic bonds. This mechanism creates physical cross-links with precisely controllable strength and density, as the valency, concentration, and type of ionic cross-linker can be systematically varied to achieve desired mechanical and responsive characteristics. The dynamic nature of these ionic cross-links, which can dissociate and reform under certain conditions, further contributes to the unique properties of ionically cross-linked hydrogels, including self-healing capabilities and stimuli-responsiveness, making them particularly valuable for applications requiring adaptable mechanical behavior. Notably, similar principles have been applied in solvent-rich systems where strong ion−polymer interactions act as effective physical cross-linkers, forming dense, tough networks through noncovalent aggregation without requiring traditional cross-linking agents.[226]

3.3.2. Particle Cross-linker. Incorporating surface modified particles into hydrogels can also facilitate effective cross-linking and subsequent polymer aggregation. Particles, ranging from 0-D nanoparticles to 3-D microgels,[227] can all serve as multifunctional cross-linkers. These particles can interact with polymer chains through hydrogen bonding[228] and ionic interactions.[229] Through these interactions, while cross-linking free polymer chains reduces the entropy of the overall system, it also lowers the enthalpy of mixing and result in forming thermodynamically stable, cross-linked networks. Kinetically, the rate of cross-linking by the particle cross-linkers is determined by the concentration of the cross-linkers and polymer, the functionality of the cross-linkers, and the reaction conditions, which in turn affect the resultant structure of the physically cross-linked network. These interactions not only contribute to the structural integrity of hydrogel but also impart new functionalities. Particle-reinforced hydrogels, such as those containing metal nanoparticles,[230] carbon nanotubes,[231] or graphene oxide,[232] exhibit improved mechanical properties[233] and electrical conductivity,[234] making them suitable for tissue engineering scaffolds,[235] sensors,[236] and actuators.[237] However, the incorporation of nanoparticles or other particles could complicate the synthesis process and potentially introduce cytotoxicity or biocompatibility issues.

Hydrogen Bonding: Jaiswal et al. presented a method for significantly enhancing the mechanical properties of collagen-based hydrogels using an ultralow concentration of surface-functionalized magnetic nanoparticles (MNPs) as a reinforcing agent.[238] The hydrogels were synthesized by incorporating oleic acid-coated iron oxide MNPs, modified with nitrodopamine-anchored PEG diacid, into a collagen solution. The MNPs act as cross-link epicenters and a nanocomposite hydrogel network is formed upon exposure to ultraviolet (UV) radiation in the presence of a photoinitiator. This method enables precise reinforcement of the hydrogel matrix by modulating the nanoparticle size and concentration, thereby influencing the density of imide bonds and carboxylate-amine interactions that form between the nanoparticles and polymer, as illustrated in Figure 8A. Introducing MNPs at a concentration 10,000 times lower than that of the polymer resulted in a more than 10-fold enhancement in mechanical stiffness and a 20-fold improvement in toughness. By adjusting the MNP size, as well as the concentrations of nanoparticles and polymer, the mechanical stiffness of the nanoengineered hydrogel could be finely tuned within a range of 0.2 to 200 kPa.

Ionic Interactions: Yu et al. created Hydrogel with Fiberboard-and-Mortar Ordered Structure (HFMOS) using ultralong hydroxyapatite (HAP) nanowires and PAA.[239] The fabrication process involves a multistep bottom-up self-assembly strategy. Ultralong HAP nanowires synthesized via a calcium oleate precursor solvothermal method are combined with PAA. The mixture is then injected into ethanol, causing the HAP nanowires to align and form a macroscale continuous fiber. These fibers are pressed into a bulk sample, which is then infused with a PAA solution to form the HFMOS hydrogel containing the COO−Ca coordination interaction between PAA molecules and ultralong HAP nanowires (Figure 8B).

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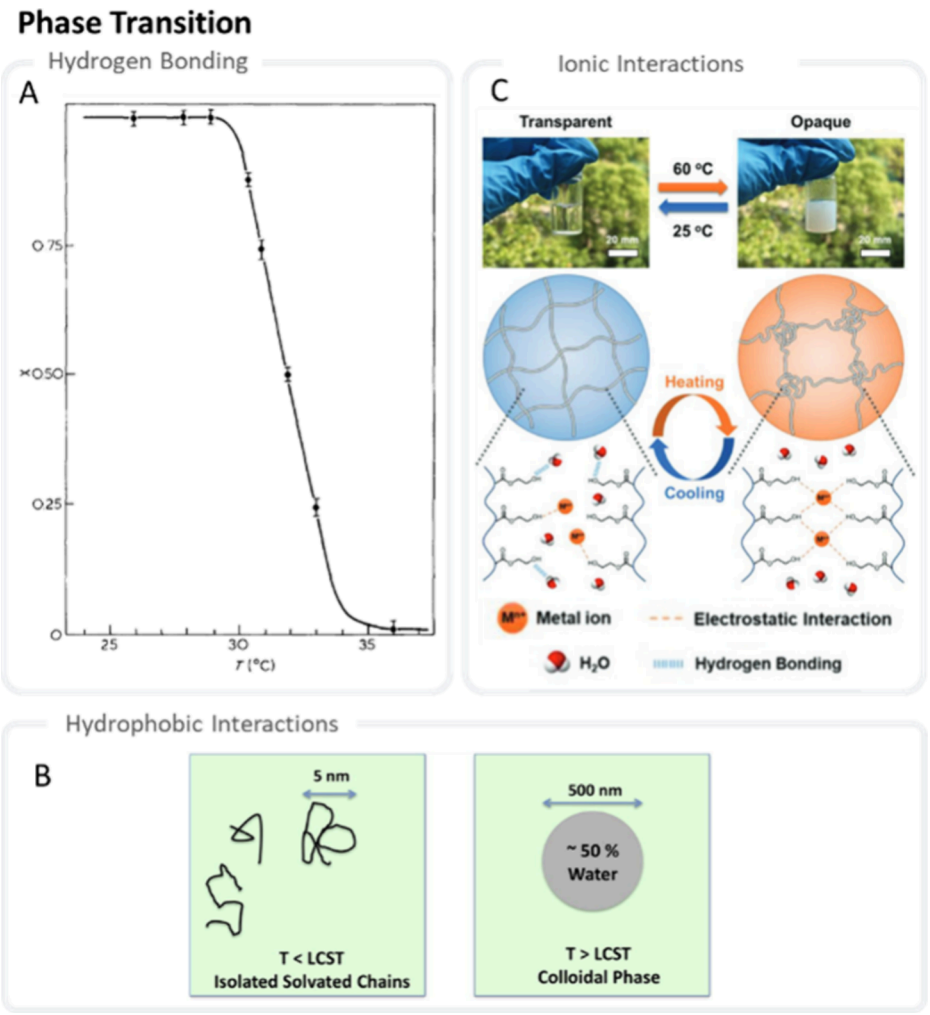

Figure 9. (A) Equilibrium melting curve of calf skin collagen in an acetic acid solution, where x is the helix amount. Reproduced with permission from ref. [244]. Copyright (1983) Elsevier. (B) Microstructure of PNIPAM below and above LCST. Reproduced with permission from ref. [95]. Copyright (2010) Elsevier. (C) Transparency change of LCST thermoresponsive hydrogels and the microstructure. Reproduced with permission from ref. [247]. Copyright (2024) Wiley.

This process results in a gel with a densely packed, hierarchically ordered structure comprising HAP nanowire-based "fiberboards" separated by PAA "mortar." The ordered assembly of HAP nanowires and their encapsulation with PAA contribute to the formation of the hydrogel's unique structure. The HAP nanowires serve as the structural backbone, providing strength and rigidity, while the PAA fills the spaces between these nanowire bundles, acting as a flexible matrix that binds the structure together. The hierarchical ordering and dense packing of the HAP nanowires within the PAA matrix results in a hydrogel with exceptional mechanical strength, high modulus, and flexibility. The structure allows for significant energy dissipation pathways, such as nanowire fracture and pull-out, contributing to its toughness. Additionally, the hydrogel demonstrates high water content, excellent rehydration capability, and can be formulated with various functionalities, including the ability to load, release, and transport functional substances.

Particle cross-linkers offer a sophisticated platform for exploiting multiple noncovalent interactions simultaneously within hydrogel networks. Hydrogen bonding plays a central role in many particle-reinforced systems, where surface-functionalized nanoparticles provide numerous sites for hydrogen bonding with polymer chains, creating multivalent physical cross-links that significantly enhance mechanical properties, as demonstrated in collagen hydrogels reinforced with PEG-modified magnetic nanoparticles. Complementing this effect, ionic interactions create additional cross-linking points as charged particles form coordination complexes with oppositely charged polymer segments, establishing strong yet dynamic bonds that contribute to structural integrity while potentially enabling self-healing characteristics. The multifunctional nature of particle cross-linkers, which can engage in multiple interaction types across their high-surface-area interfaces, enables the creation of hydrogel composites with synergistically enhanced properties that often surpass the capabilities of conventional cross-linking approaches.

3.3.3. Operational Windows and Precautions. Cross-linker-induced aggregation requires careful balancing of cross-linker concentration and addition rate to achieve uniform network formation. For alginate systems, calcium concentrations of 0.05−0.2 M are normally used for ionic cross-linking. However, by using a two-step diffusion method with a covalently precross-linked alginate−gelatin network, a Ca^{2+} concentration as high as 3.0 M can be applied to achieve enhanced ion incorporation (∼7 wt %). Concentrations or

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Chem. Rev. XXXX, XXX, XXX−XXX

immersion durations beyond this can lead to hydrogel swelling, degradation, and decreased mechanical performance due to Ca^{2+} leaching and oversoftening of the network.[240] The most critical precaution is maintaining appropriate pH and ionic strength to ensure optimal ionization states of the polymer functional groups that participate in cross-linking interactions.

3.4. Phase Transition

For hydrogels constructed from polymers that exhibit phase transition properties, instead of tuning solvation or adding physical cross-linkers, we can increase polymer−polymer interactions by applying an external stimulus that triggers its phase change to induce aggregation. In many cases the stimulus is a change in the temperature. The aggregation behavior of hydrogels in response to temperature changes is primarily driven by the balance between hydrophilic and hydrophobic interactions within the polymer network. Two main representations of this temperature responsiveness are Lower Critical Solution Temperature (LCST) behavior, where the hydrogels exhibit increased hydrophobicity and aggregation above a certain temperature, and Upper Critical Solution Temperature (UCST) behavior, where hydrogels become more hydrophilic and less aggregated as the temperature increases.[241] Both LCST and UCST transitions involve balancing enthalpic and entropic contributions to minimize free energy in the aggregated state.[242] For LCST behavior, at temperatures above LCST, the entropy gain from mixing is overcome by the enthalpy driven phase separation, leading to aggregation. The rate of phase separation is affected by the rate which temperature approaches or surpasses critical temperatures. Thermal hysteresis where phase separation temperature is different with dissolution temperature can be caused by rapid temperature change or certain thermal history. Temperature-responsive hydrogels allow for precise control over material behavior, which is particularly useful for applications like drug delivery, where temperature changes can trigger release.[243] However, the requirement for temperature control can limit practical applications and may necessitate additional infrastructure to maintain specific temperatures.

Hydrogen Bonding: Djabourov et al. examined the effect of various thermal treatments on gelatin gel formation and their structural changes.[244] The gelatin gels are prepared by dissolving gelatin in water followed by different thermal treatments, including controlled cooling and heating rates and quenching, followed by prolonged annealing. Temperature can influence the aggregation of gelation because it can disrupt hydrogen bonds between gelatin molecules, leading to structural modifications.[245] The study reveals that the transition from helix to coil structures in gelatin is sensitive to temperature changes, with the formation of helices upon cooling contributing to the network's growth, as shown in Figure 9A. The structural changes induced by thermal treatments lead to variations in the gel's properties, such as its elasticity and stability.

Hydrophobic Interactions: Pelton et al. investigated the origin of thermal responsive behavior of PNIPAM entailing the coexistence of hydrophobic and hydrophilic domains at all temperatures.[246] As depicted in Figure 9B, below the LCST, the isopropyl groups (hydrophobic domains) of PNIPAM are surrounded by water, making them less accessible. Above the LCST, although PNIPAM aggregates and reduces its solubility in water, the aggregated phase still contains a significant amount of water, indicating that it does not become entirely hydrophobic. Instead, the aggregates are formed due to the reduced solubility of only the hydrophobic segments of PNIPAM in water. This aggregation then leads to phase-separated structures that range from colloidal particles to continuous macroscopic precipitates, depending on the concentration of the solution.

Ionic Interactions: Zhou et al. demonstrated that the addition of aluminum chloride ($AlCl_3$) to nonresponsive poly(2-hydroxyethyl acrylate) (PHEA) hydrogels can induce a reversible thermoresponsive behavior.[247] The PHEA-Al hydrogels are fabricated by dissolving 2-hydroxyethyl acrylate (HEA) in an aluminum chloride ($AlCl_3$) aqueous solution, followed by nitrogen degassing, the addition of an initiator and cross-linker, and subsequent polymerization under UV light. The formation of the hydrogel is driven by electrostatic interactions between the hydroxy groups of the polymer and trivalent metal ions, leading to a material that shows significant thermoresponsive behavior. As shown in Figure 9C, upon heating, the cation-dipole interactions between Al^{3+} ions and PHEA's hydroxy groups strengthen, repelling water molecules and causing the hydrogel to transition from a transparent to an opaque state. The study highlights the unique role of electrostatic interactions in achieving thermoresponsive behavior, deviating from the conventional reliance on hydrophobic interactions in such materials.

Phase transition methods in hydrogel engineering harness temperature-dependent behaviors of multiple noncovalent interactions to create responsive materials with tunable properties. Hydrogen bonding undergoes significant changes during thermal transitions, as temperature fluctuations directly alter both the strength and number of hydrogen bonds formed between polymer chains, elegantly demonstrated in gelatin systems where cooling promotes helix formation stabilized by hydrogen bonds. Hydrophobic interactions exhibit particularly dramatic temperature dependence, serving as the primary driving force in temperature-responsive polymers like PNIPAM, where the delicate thermodynamic balance between entropic and enthalpic contributions shifts above the LCST, triggering hydrophobically driven chain aggregation and volume phase transitions. Additionally, ionic interactions respond to thermal changes as temperature variations modulate the strength of ion-dipole interactions in systems like PHEA-Al hydrogels, where heating strengthens cation-dipole interactions between Al^{3+} ions and polymer hydroxy groups. This orchestrated response of multiple interaction types to temperature changes enables the design of sophisticated stimuli-responsive hydrogels with programmable behavior for diverse applications.

3.4.1. Operational Windows and Precautions.

The effectiveness of phase transition methods depends on precisely controlling the trigger intensity for the aggregation process. For the gelatin hydrogel system, the thermally induced helix aggregation gelation happens with temperature between 10 and 40 °C. Outside this range, the system either fails to form stable helices at higher temperatures ($T > 40$ °C), resulting in melting, or forms disordered and rapidly aggregated structures at very low temperatures ($T < 10$ °C).[244] The main precaution is avoiding temperature overshooting beyond the transition point, which can lead to irreversible aggregation or collapse that prevents the formation of ordered structures.

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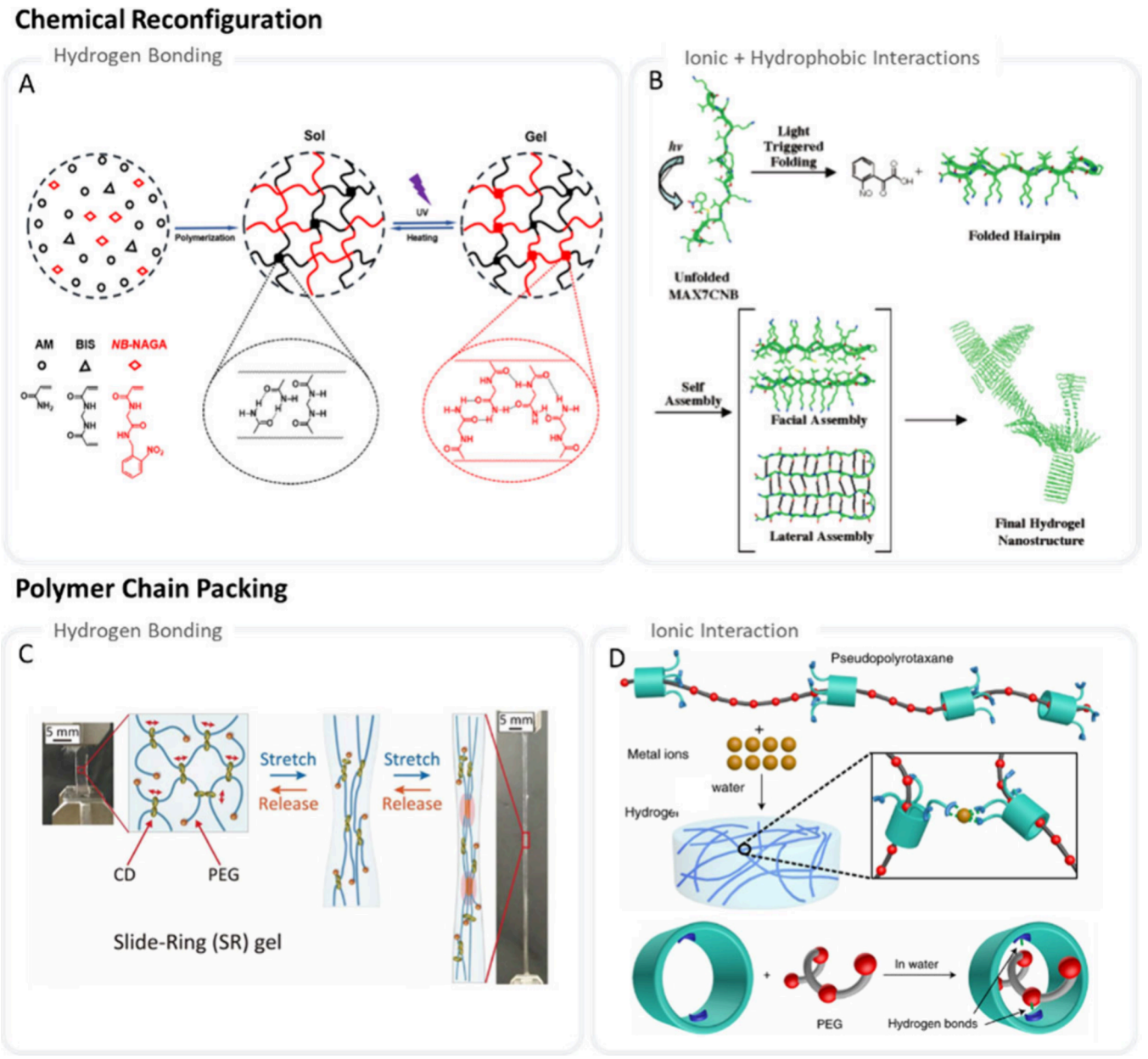

Figure 10. (A) Schematic illustration of hydrogel fabricated by photoinduced gelation through hydrogen bonding. Reproduced with permission from ref. [254]. Copyright (2020) Springer. (B) Formation of materials induced by light. Reproduced with permission from ref. [255]. Copyright (2005) American Chemical Society. (C) Schematic representation of samples and reinforcement strategy. Reproduced with permission from ref. [260]. Copyright (2021) Science. (D) General view of the gelation process. Reproduced with permission from ref. [261]. Copyright (2019) Nature Publishing Group.

3.5. Chemical Reconfiguration

The polymer−polymer interaction in hydrogels could also be increased when the functional groups are modified in situ. For instance, light can be used to trigger aggregation in photoresponsive polymers. These polymers contain functional groups that change their configuration,[248] polarity,[249] hydrophilicity,[250] or solvent−polymer interaction achieved by either isomerization or ionization upon exposure to light. The isomerization or ionization rate is influenced by light intensity and the degree of overlap between photon energy and the polymer's energy bands. Additionally, the aggregation process is impacted by the photostability of the polymers when subjected to prolonged light exposure. Polymers containing azobenzenes[251] and spiropyran[252] as the chromophore are the most widely studied photoresponsive polymers. Light-induced aggregation offers spatial and temporal control over hydrogel properties, ideal for applications requiring precise activation like controlled drug release.[253] The main drawback is the need for specialized equipment to deliver the appropriate light stimulus, which can add complexity and cost to material fabrication.

Hydrogen Bonding: Zhang et al. developed a unique hydrogel that reconfigures through photoinduced cleavage.[254] The hydrogel is synthesized through a reversible addition−fragmentation chain transfer (RAFT) polymerization process using acrylamide, N'-(2-nitrobenzyl)-*N*-acryloyl glycinamide (NBNAGA), and N,N'-methylene bis-acrylamide (BIS) as the cross-linker. The resulting polymer solution is initially viscous,

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Chem. Rev. XXXX, XXX, XXX−XXX

transparent, and flowable, containing only weak hydrogen bonding and sparse chemical cross-linking. Upon UV (365 nm) light exposure, the o-nitrobenzyl groups attached to the NBNAGA within the hydrogel are cleaved, resulting in the formation of 'uncaged' dual amide groups, as shown in Figure 10A. The newly formed functional groups triggers the formation of dual hydrogen bonds among the amide moieties, which promote the transition of the polymer solution into a robust hydrogel. The hydrogel demonstrates significant temperature sensitivity and self-healing properties due to its dynamic hydrogen bonding.

Ionic + Hydrophobic Interactions: Haines et al. explores the novel synthesis of a light-responsive hydrogel using a peptide amphiphile, MAX7CNB, which contains a photocleavable protecting group that prevents the peptide from folding and assembling into a gel structure under ambient light. Figure 10B shows the process of material formation. Upon exposure to UV light (wavelengths between 260 and 360 nm), the protecting group is removed, allowing the peptide to fold into an amphiphilic β-hairpin structure. This folding promotes self-assembly into a mechanically rigid hydrogel via hydrophobic interactions and hydrogen bonding between the peptide molecules.[255] Upon light activation, the hydrogel shows increased stiffness with a storage modulus of around 1000 Pa. This stiffening is a result of the dense cross-linking of the peptide hairpins within the hydrogel matrix. The hydrogel is also noncytotoxic and supports cell adhesion and proliferation.

Stereoselective Interactions: Chemical reconfiguration can dynamically modulate stereoselective interactions by triggering conformational changes that expose or create chiral binding sites. Photoresponsive systems, for instance, employ light-induced isomerization of functional groups to switch between different stereochemical configurations, thereby enabling or disabling stereoselective binding.[256] These adaptable stereoselective interactions are particularly valuable in controlled drug delivery and bioengineering, where external stimuli can modulate material behavior. However, achieving precise control over stereochemical switching necessitates meticulous molecular design and fine-tuning of the photochemical response.

Chemical reconfiguration strategies enable unprecedented control over noncovalent interactions in hydrogel systems through externally triggered molecular transformations. Hydrogen bonding networks can be dynamically generated or disrupted through phototriggered processes that create new hydrogen bonding sites or alter existing ones, as elegantly demonstrated in NBNAGA-based hydrogels where UV irradiation cleaves protective groups to reveal dual amide moieties capable of forming strong hydrogen bonds. Hydrophobic interactions are similarly manipulated through light-induced conformational changes that strategically expose or conceal hydrophobic domains, enabling precise spatial and temporal control over hydrophobically driven aggregation processes. Perhaps most sophisticatedly, stereoselective interactions can be dynamically modulated as photoresponsive moieties undergo isomerization or cleavage reactions that enable or disable stereoselective binding sites, creating chiral recognition capabilities that can be activated on demand. This ability to precisely control multiple interaction types through external stimuli provides unparalleled opportunities for creating programmable hydrogels with spatiotemporally controlled properties for advanced applications.

3.5.1. Operational Windows and Precautions.

Chemical reconfiguration methods rely on precisely controlling the stimulus intensity and duration to achieve the desired extent of structural change. For photochemical approaches, the wavelength must match the absorption spectrum of the photoactive group, while the light intensity must be sufficient to trigger the reaction without causing damage to other components. Azobenzene-containing PEG hydrogels require precise light control, with Nehls et al. demonstrating that optimal reversible modulation of hydrogel stiffness occurs at 365 nm (UV) and 400−500 nm (visible) with intensities of 10 mW/cm^2. Higher intensities exceeding cytocompatible levels could potentially cause cell damage or unintended photochemical side reactions.[257] The primary precaution is managing unwanted side reactions, particularly in radical-based systems where oxygen can act as an inhibitor or in systems where heat generated during the process can trigger unintended thermal responses.

3.6. Polymer Chain Packing

Further alternative ways to boost polymer−polymer interactions would involve mechanically packing the polymer chains in existing hydrogels. Mechanical force, such as stretching of polymer chains, can facilitate interchain interactions and the formation of crystallites, further inducing aggregation. When the polymer chains are stretched, chain alignment and closer packing are promoted. The conformational entropy is reduced, while the crystalline state is more energetically favorable due to the ordered arrangement and strong intermolecular interactions.[258] The final aggregated structure is influenced by the strain rate. Rapid stretching will result in less ordered structure and residual stress, creating more defects in the material.[259] Using mechanical force to induce aggregation can enhance the toughness and resilience of hydrogels, making them suitable for applications where mechanical integrity is crucial. However, the requirement for mechanical input can limit the practicality of this method in some applications, and repeated mechanical stress might lead to material fatigue over time.

Hydrogen Bonding: Liu et al. developed slide-ring (SR) hydrogels that demonstrate remarkable toughness and rapid self-reinforcement capabilities under mechanical force.[260] SR hydrogels are fabricated by mixing PEG with hydroxypropyl-a-cyclodextrin (CD), which are linked covalently by divinyl sulfone (DVS). This structure allows the CDs to slide along the PEG chains, enabling the hydrogels to adapt and reorganize under strain. Figure 10C depicts the self-reinforcement process. Upon uniaxial stretching, the SR hydrogels undergo strain-induced crystallization. As the hydrogel is stretched, the slidable cross-links allow the PEG chains to become highly oriented and closely packed, leading to the formation of crystalline structures. The crystalline domains form rapidly under strain and is reversed upon release, contributing to the hydrogel's exceptional mechanical properties. The primary property exhibited by the SR hydrogels is their significant toughness, with values reaching up to 22 MJ/m^3, far surpassing those of conventional covalently cross-linked gels. Additionally, the hydrogels demonstrate excellent recoverability and durability over repeated loading−unloading cycles, showing almost no residual strain and maintaining consistent mechanical responses.

Ionic Interactions: Ke et al. presented an innovative approach to hydrogel fabrication where shear force is utilized to induce hydrogel formation.[261] The hydrogel is fabricated by

https://doi.org/10.1021/acs.chemrev.5c00069
Chem. Rev. XXXX, XXX, XXX−XXX

first mixing molecular tubes with PEG to create pseudopolyrotaxanes. Then, copper(II) nitrate [$Cu(NO_3)_2$] is added, facilitating cross-linking through the coordination of the carboxylate groups on the molecular tubes. This mixture remains in a sol state until shear force transforms it into a gel. As shown in Figure 10D, when shear force is applied via shaking, it induces a transition from intrachain to interchain coordination among the pseudopolyrotaxanes. This mechanical stimulation alters the molecular interactions within the gel, shifting from a predominantly linear alignment to a networked cross-linking, which stabilizes the gel structure. This gelation process is reversible, with the hydrogel able to relax back to the sol state over time or under specific conditions like increased temperature or further shaking.

Mechanical force-induced polymer chain packing represents a unique approach to enhancing noncovalent interactions through physical alignment and spatial reorganization. Hydrogen bonding efficiency is substantially improved through mechanical stretching, which aligns polymer chains in preferred orientations, significantly facilitating hydrogen bond formation between adjacent chains and creating mechanically robust domains with enhanced structural ordering, as demonstrated in PVA hydrogels where stretching induces strain-crystallization stabilized by hydrogen bonds. Concurrently, ionic interactions undergo mechanical activation as applied forces strategically convert intramolecular ionic bonds to intermolecular cross-links, effectively transforming self-interactions into network-strengthening bridges between chains, exemplified in shear-induced gelation of pseudopolyrotaxanes through coordination-bond reorganization. This mechanical manipulation of noncovalent interactions offers distinct advantages for creating anisotropic hydrogels with directionally enhanced properties, particularly valuable for applications requiring biomimetic structures that emulate the aligned architectures found in natural tissues.

3.6.1. Operational Windows and Precautions. Mechanical force-induced aggregation effectiveness depends primarily on applying sufficient strain to induce chain alignment while preventing material failure. PVA−tannic acid hydrogels undergoing mechanical alignment are highly sensitive to both strain and strain rate. Optimal crystallization and alignment occur under large tensile strains between 200% and 800%, applied at a moderate strain rate (e.g., ∼ 100 mm/min as used in this study). Applying excessively high strain rates may inhibit molecular alignment or lead to premature failure, reducing the effectiveness of the structural ordering process.[262] The temperature during deformation significantly influences chain mobility and the resulting degree of crystallinity, with optimal conditions typically occurring between the glass transition temperature and melting point of the polymer. The key precaution is ensuring uniform force distribution throughout the material to prevent localized stress concentration that can lead to premature failure before ordered structures can form.

3.7. Combined Strategy Approaches

Multiple aggregation methods can be synergistically combined to achieve properties impossible with single approaches. For example, cononsolvency with subsequent freeze−thaw cycling creates highly structured PVA hydrogels with enhanced mechanical properties and antifreezing capabilities;[29] sequential ionic cross-linking followed by directional freezing produces alginate hydrogels with aligned microchannels for tissue engineering;[160] photosensitive moieties incorporated into LCST polymers enable orthogonal control through both light and temperature; and mechanical stretching combined with salt treatments significantly enhances crystallinity and mechanical properties in PVA/tannic acid systems.[262] These combinatorial approaches represent a powerful frontier in hydrogel design, enabling unprecedented control over structure and function across multiple length scales.

3.8. Cross-Cutting Behaviors of Noncovalent Interactions across Aggregation Methods

This section examines how the same noncovalent interaction changes its behavior, strength, and functions when triggered by different aggregation methods, highlighting the versatility of these interactions and providing insights for strategic hydrogel design.

3.8.1. Hydrogen Bonding. Hydrogen bonding exhibits remarkable adaptability across different induction routes. In self-assembly, hydrogen bonds form gradually and reach equilibrium structures, while in solvent perturbation, they form rapidly and with higher density as solvent molecules are excluded. The strength of hydrogen bonds remains relatively constant in both cases, but their number and arrangement differ significantly. Phase transitions introduce temperature-dependence more pronounced than other methods—hydrogen bonds can strengthen upon cooling or, counterintuitively, upon heating. Meanwhile, chemical reconfiguration enables ″switching″ hydrogen bonds from nonexistent to fully formed through stimuli, creating binary rather than gradual activation unlike other methods. Mechanically induced hydrogen bonding uniquely creates anisotropic networks with directional properties, unlike the more isotropic networks formed through other routes.

3.8.2. Hydrophobic Interactions. Hydrophobic interactions demonstrate environment-sensitive behavior that varies markedly between aggregation methods. In self-assembly, these interactions drive micelle formation through modest entropic gains, while in solvent perturbation, particularly with nonsolvents or salting-out, they intensify dramatically as water structure around hydrophobic groups is disrupted. Unlike other interactions, hydrophobic forces uniquely strengthen with temperature increases in LCST systems, contrary to their behavior in self-assembly where increased temperature typically weakens aggregation. Cross-linker-induced hydrophobic aggregation often creates localized domains around cross-link points rather than the extended networks seen in phase separation. Chemical reconfiguration can transform hydrophilic regions into hydrophobic ones instantaneously, unlike the gradual transitions in other methods. Under mechanical force, hydrophobic domains align and pack more efficiently than possible through thermal motion alone, creating stronger interactions than achievable through environmental triggers.

3.8.3. Ionic Interactions. Ionic interactions show particularly diverse behavior across induction methods. In self-assembly, these interactions depend primarily on charge density and distribution, while in solvent perturbation (especially ion-specific effects), the same ionic groups interact differently depending on the specific ions present—kosmotropes and chaotropes producing opposite effects on the same polymer. Cross-linker addition creates ionic bridges that are typically stronger and more structured than self-assembled ionic networks, with multivalent ions creating distinctive

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Chem. Rev. XXXX, XXX, XXX−XXX

coordination geometries. During pH-induced aggregation, ionic interactions progressively strengthen or weaken along a continuum rather than the binary on/off behavior observed in light-triggered chemical reconfiguration. Temperature changes in phase transitions affect ionic interactions primarily through changes in dielectric constant, while mechanical forces can reconfigure ionic bonds from intramolecular to intermolecular forms—a transformation unique to this induction method.

3.8.4. π-π Interactions. π-π interactions display varying stacking geometries and strengths when triggered by different methods. Self-assembly typically results in thermodynamically favored parallel-displaced or T-shaped arrangements, while solvent perturbation can force face-centered stacking as solvation shells are disrupted. Temperature changes during phase transitions affect π-π stacking primarily through altered electron distribution rather than through structural reorganization as seen in mechanical packing. Chemical reconfiguration can alter π-π interactions by transforming nonplanar structures into planar aromatic systems through isomerization, a mechanism unavailable in other induction methods. The strength of π-π interactions in cross-linker systems depends heavily on the specific coordination environment created by the cross-linker, unlike the more uniform stacking arrangements in self-assembled systems.

3.8.5. Host−Guest Interactions. Host−guest interactions demonstrate method-dependent selectivity and binding kinetics. In self-assembly, these interactions are primarily driven by shape complementarity and hydrophobic effects, while solvent perturbation can enhance binding through dehydration of the host cavity. Temperature changes during phase transitions alter binding constants through entropy-enthalpy compensation, creating temperature-sensitive complexation not observed in cross-linker-induced systems. Chemical reconfiguration can alter host cavity size or guest binding affinity through conformational changes, enabling selective guest release not possible in self-assembled systems. Mechanical force can distort host cavities or thread guest molecules through barriers that would be insurmountable under equilibrium conditions, creating nonequilibrium complexes with unique binding profiles compared to those formed through other aggregation methods.

3.8.6. Stereoselective Interactions. Stereoselective interactions exhibit distinct behaviors across different induction routes due to their reliance on molecular chirality and precise spatial arrangement. In self-assembly, stereoselective interactions are primarily dictated by inherent chiral recognition mechanisms, such as the Watson−Crick base-pairing in DNA hydrogels, where complementary chiral interactions drive the formation of highly specific and stable structures. Chemical reconfiguration offers an avenue for actively controlling stereoselective interactions, as photoresponsive systems can switch between different stereochemical states upon light exposure, dynamically modulating molecular recognition sites. However, some other methods, such as mechanical force, addition of cross-linker and solvent perturbation typically has a weaker influence on stereoselective interactions.

The analysis of how different noncovalent interactions behave across various aggregation methods highlights the importance of strategically combining both the right interactions and the appropriate induction techniques. While Section 2.3 established the theoretical importance of mixed interactions, this practical examination demonstrates how researchers can leverage these interactions in real hydrogel systems. By understanding both the fundamental chemistry of these interactions and their method-dependent behaviors, researchers can design hydrogels with unprecedented control over structure, properties, and functionality.

4. ENGINEERING AGGREGATED STRUCTURES FOR IDEAL PROPERTIES

Hydrogels face numerous demands in applications on their microstructural, mechanical, mass transport, swelling, stimuli responsive and adhesive properties, which are pertinent to the physical, chemical, biochemical, biomechanical, and electrochemical conditions they serve in.[263] Harnessing the strategies of inducing aggregation as discussed above, hydrogels can be structurally engineered and programmed to meet those demands. For instance, aggregation manifests as driving force for the reconfiguration of pore size and formfactor in hydrogels, leading to vital changes of nutrient transport properties for tissue scaffold applications.[264] Likewise, the similar microstructural change may impact cross-link densities and material anisotropy, which is crucial for modulating the mechanical properties of hydrogels for biomedical applications.[265] Often, a combination of hydrogel properties must coincide in one matrix and a combination of microstructures is needed to optimize hydrogel performance. This further necessitates the understanding of the simultaneous impact of selected microstructures on the array of target properties and other existing microstructures. In general, the length scale, density, anisotropy and spatial orientation of aggregated structures determines the combined properties of hydrogel and are wisely utilized to drive forward hydrogel application in respective fields.

Different noncovalent interactions and aggregation methods possess unique strengths and limitations that must be carefully matched to application requirements (Table 3). When designing hydrogels, researchers must consider not only the desired properties but also the inherent trade-offs associated with each approach. For instance, hydrogen bonding-based systems like PVA/tannic acid (TA) hydrogels demonstrate exceptional mechanical strength (up to 750 MPa) through dense physical cross-linking, making them ideal for load-bearing tissue engineering applications where mechanical integrity is paramount, but their reduced swelling capacity limits their utility in drug delivery applications.[262] Conversely, hydrogels utilizing hydrophobic interactions, such as PNIPAM-based systems, exhibit dramatic responsiveness to temperature changes with sharp volume transitions, making them excellent candidates for controlled drug release and soft actuators, but their limited mechanical strength (typically <1 MPa) renders them unsuitable for applications requiring significant load-bearing capacity. Similarly, ionic interaction-based systems like polyampholyte gels offer exceptional toughness and self-healing properties through sacrificial bonds that efficiently dissipate energy, positioning them well for biomechanical interfaces that experience repeated deformation, yet their performance can deteriorate under extreme pH conditions.[122] The successful engineering of hydrogels thus requires careful consideration of both the desired functionality and the limitations imposed by the selected noncovalent interactions and aggregation methods.

4.1. Tissue Engineering

Tissue engineering is an interdisciplinary field that combines scaffolds, cells, and biologically active molecules to develop

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Chem. Rev. XXXX, XXX, XXX−XXX

Table 3. Application-Specific Requirements and Preferred Noncovalent Interactions and Aggregation Methods for Hydrogel Systems

Applications	Key Property Requirements	Criteria for Noncovalent Interactions	Preferred Noncovalent Interactions	Criteria for Aggregation Methods	Preferred Aggregation Methods
Tissue Engineering	Mechanical match with tissue, Biocompatibility	Operate under physiological conditions, Mechanical match, Support pore structure	Hydrogen bonding, Ionic interactions, Hydrophobic interactions, Host−guest complexation	Preserve cell viability, Create appropriate porosity, Create appropriate mechanical properties	Ice templating, Ionic cross-linking, Phase separation, Self-assembly
Drug Delivery	Controlled swelling, Tunable release kinetics	Preserve drug effectiveness, Enable controlled release	Hydrogen bonding, Hydrophobic interactions, Host−guest interactions, Ionic interactions	Preserve therapeutic agent stability, Enable precise control over release kinetics	pH-responsive aggregation, Temperature transition, Ionotropic gelation, Phase separation
Soft Electronics	High ionic conductivity, Mechanical durability	Enable high ionic conductivity, Mechanical durability, Environmental stability	Hydrogen bonding, Ionic interactions, Hydrophobic associations	Ion pathway preservation, Mechanical robustness	Freeze−thaw cycling, Salting-out, Controlled phase separation, Cononsolvency
Sensors/Actuators	Fast response, Reversible transitions	Reversible, Fast response rate, High cycling stability, Strong stimulus-response coupling	Hydrogen bonding, Ionic interactions, Host−guest interactions	Produce structures with rapid, reversible responses	Temperature-induced, Light-triggered, pH-responsive, Ion-induced
Wound Dressing	Adhesion control, Exudate management	Support healing, Provide adhesion, Manage exudate	Ionic interactions, Hydrogen bonding, Hydrophobic interactions	Produce structures balancing adhesion with exudate management and antimicrobial properties	Ionic cross-linking, Temperature-responsive, Phase separation

tissue substitutes, support tissue repair, or enhance existing tissues.[266] Naturally occurring tissues exhibit a complex array of functional-critical mechanical properties that are directly tied to the microstructures formed via aggregation of biocomponents. These properties include stiffness, strength, and viscoelastic behavior.[267] For instance, tendons are relatively stiff and elastic as a force transferring component, with a Young's modulus ranging from 0.5 to 1.5 GPa and toughness between 50 and 150 MJ/m.[3,268] Cartilage, on the other hand, has a Young's modulus between 0.1 and 1 MPa and a toughness between 5 and 10 MJ/m^3, but are viscoelastic to deform and absorb impacts at joints.[269] These two collagen rich tissues exhibit drastically different properties, exclusively depending on the cross-link density, porosity and alignment of the extra-cellular materials. To mimic the structure and functionalities of biological matrix, common substitutes include natural polymers such as collagen, alginate, proteoglycans, and chitosan.[270] These materials are preferred due to their ability to promote cell adhesion and proliferation, alongside their exemplary biocompatibility, biodegradability, and bioactivity.[49] Yet, mechanical properties are paramount in such applications, as hydrogels must provide robust structural support during the cell-based tissue formation process as well as precisely mimicking the stiffness, viscoelastic behavior of the replaced tissues.[271] Conventional hydrogels typically offer high water content and biocompatibility, but often lack the tunability to serve in various tissue engineering applications. Thus, methods and techniques that utilizes noncovalent aggregation to fine-tune hydrogel microstructure and mechanics are of vital importance in creating scaffolds that are compatible with cells while achieving desired functionalities.

4.1.1. Selection Criteria for Tissue Engineering Applications. *4.1.1.1. Noncovalent Interactions and Selection Criteria.* Tissue engineering hydrogels require noncovalent interactions that operate under physiological conditions while creating matrices with appropriate mechanical properties and porosity. Hydrogen bonding provides reversible cross-links essential for cell-mediated matrix remodelling, allowing cells to migrate and reorganize their environment while maintaining structural integrity.[272] Ionic interactions between carboxylate groups and divalent cations create strong yet cell-responsive networks that promote cell attachment while resisting enzymatic degradation.[273] Hydrophobic interactions contribute structural stability and responsiveness to physiological stimuli, creating domains that provide mechanical reinforcement and cell-recognition sites.[274] Host−guest interactions offer precise control over local mechanical properties and degradation profiles through selective molecular recognition. In modern tissue scaffolds, these interactions work synergistically to recapitulate the hierarchical organization of natural tissues, with different bond types providing complementary functions that balance mechanical support with biological activity.

4.1.1.2. Aggregation Methods and Selection Criteria. Tissue engineering requires aggregation methods that preserve cell viability during matrix formation while creating structures with appropriate porosity and mechanical properties. Effective methods include: ice templating, which creates aligned porous structures through controlled ice crystal growth that guides cell alignment and matrix organization—ideal for engineering anisotropic tissues like muscle or tendon; ionic cross-linking, which forms hydrogels under physiological conditions (pH 6.5−7.5) without toxic byproducts, enabling cell encapsulation

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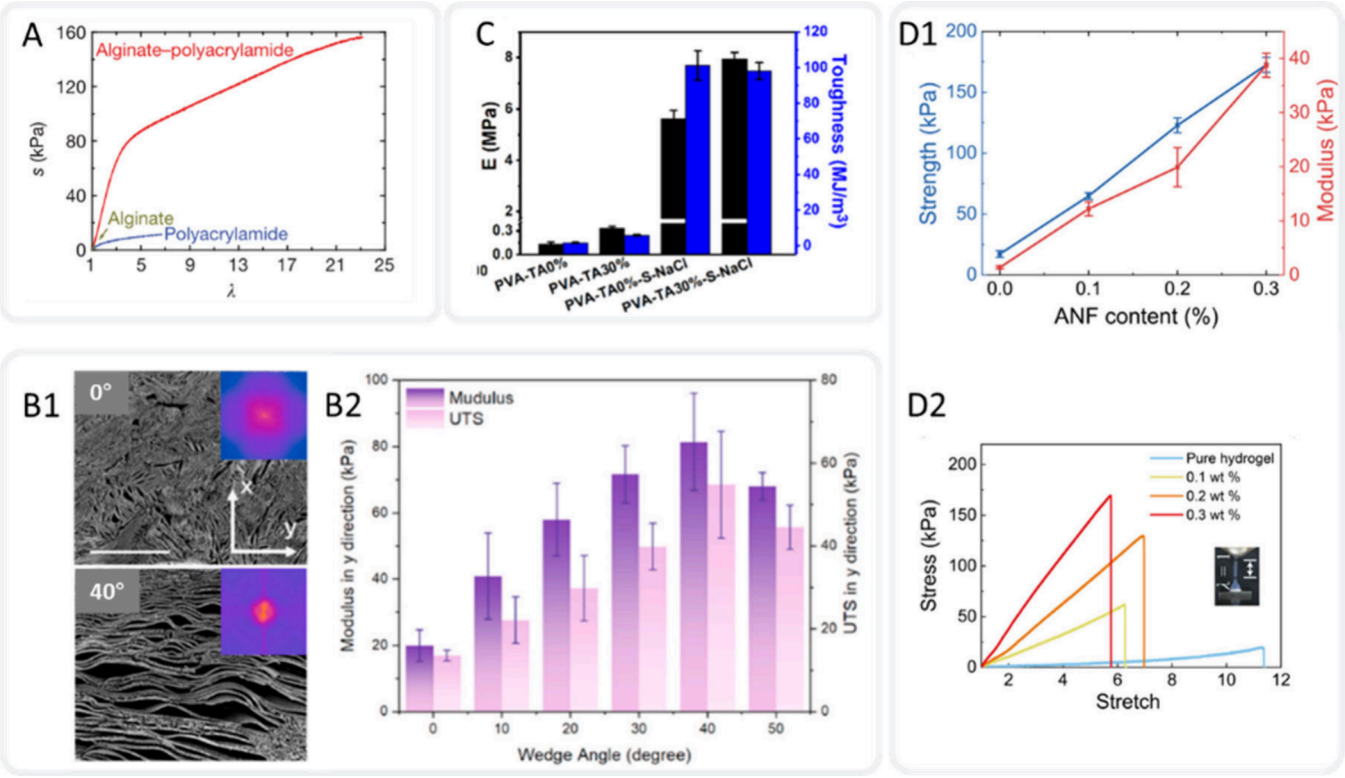

Figure 11. (A) Nominal stress–stretch curves for the dual-network and single-network hydrogels. Reproduced with permission from ref. [13]. Copyright (2012) Nature Publishing Group. (B1) SEM images of x–y planes illustrating the lamellar orientations of structures fabricated at varying wedge angles, with corresponding Fourier-transformed images shown as insets. Scale bars: 1 mm. (B2) Tensile modulus and ultimate tensile strength (UTS) of anisotropic PVA gels measured along the y-direction. Reproduced with permission from ref. [290]. Copyright (2022) Elsevier. (C) Elastic moduli and toughness of PVA-TA hydrogels. Reproduced with permission from ref. [262]. Copyright (2019) American Chemical Society. (D1) Effect of ANF concentration on strength and modulus. (D2) Stress–stretch curves of selected as-prepared samples, with the inset displaying the initial condition of a 0.2 wt % ANF-hydrogel composite under uniaxial stretching. Reproduced with permission from ref. [293]. Copyright (2023) Elsevier.

with high viability during fabrication;[275] controlled phase separation, which generates interconnected pore networks with tunable architecture through thermodynamically driven demixing processes that yield structures supporting both cell migration and nutrient diffusion;[276] and self-assembly, which creates nanofibrillar networks mimicking native extracellular matrix through spontaneous organization of amphiphilic molecules under mild conditions.[277] Each method addresses specific tissue engineering requirements: ice templating provides the structural anisotropy essential for mechanically functional tissues, ionic cross-linking offers the cytocompatible conditions necessary for cell incorporation, phase separation creates the interconnected porosity required for cell infiltration and vascularization, and self-assembly generates the nanoscale features that guide cell adhesion and differentiation—collectively enabling the fabrication of sophisticated tissue constructs with hierarchical organization spanning from molecular to macroscopic scale.[278]

4.1.2. Tuning Physical Cross-link Density. Tunning the number of cross-links is one of the most direct and effective strategies for optimizing the mechanical properties of hydrogels. Cross-linking density is defined as the number of cross-linker segments in a unit volume of material. Higher physical cross-link density via noncovalent interactions would induce aggregation that leads to denser regions within the hydrogel, affecting swelling behavior and mechanical properties.[38] Cross-link density significantly influences the Young's modulus of hydrogels. For a hydrogel with noncovalent interactions between polymer chains, the Young's modulus can be expressed as

$$E = E_{pr} + E(\dot{\varepsilon}) \tag{6}$$

Where $\dot{\varepsilon}$ is the strain rate, E_{pr} is the elastic modulus of the primary covalently cross-linked network, and $E(\dot{\varepsilon})$ is the strain rate dependent component of the elastic modulus that comes from the noncovalent interactions. The increase of cross-linking density by noncovalent interactions mostly enhances the second term, especially at higher strain rates.[279]

The elastic modulus can be enhanced by aggregation of polymer chains induced by various stimuli such as solvents, ions, particles, or pH. In the work by Jin et al., the mechanical characteristics of poly(methacrylamide) (PMAm) hydrogel can be precisely adjusted across a wide spectrum by perturbation of polymer solvation with various salt ions. The salt-induced aggregation of PMAm hydrogels creates heterogeneous domains of densely cross-linked polymer regions interspersed with less cross-linked regions. These nanoscale ionic clusters act as reversible physical cross-links, where the size and density of these clusters directly correlate with modulus enhancement, with higher salt concentrations producing more numerous and larger aggregation domains. Based on this method, Young's modulus can be finely tuned, ranging from 10^{-2} to 10^{3} MPa.[280]

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Chem. Rev. XXXX, XXX, XXX–XXX

Apart from modulus, toughness is also an important mechanical property that can be tuned by adjusting cross-link density. Toughness can be characterized by fracture energy Γ, which is defined as the amount of energy absorbed to create a unit area of a crack. The total fracture energy of hydrogels with noncovalent interactions can be calculated by this equation:

$$\Gamma = \Gamma_0 + \Gamma_D \quad (7)$$

where Γ_0 is the intrinsic fracture energy for breaking covalently cross-linked polymer chains bridging, and Γ_D is the fracture energy that comes from energy dissipation from the breakage of the sacrificial noncovalent bonds.[281]

Upon application of stress, the presence of sacrificial bonds enables a redistribution of mechanical forces at the molecular level. Instead of localizing stress, which can lead to failure, the stress is spread more evenly throughout the material. This redistribution helps prevent the formation of catastrophic cracks and enhances toughness. Hydrogels with sacrificial bonds often incorporate a hybrid network structure, combining both covalent (permanent) and noncovalent (reversible) cross-links. The covalent cross-links provide the hydrogel with structural integrity and stretchability, while the noncovalent, sacrificial bonds offer the ability to dissipate energy. After the initial sacrificial bonds break, the hydrogel can still maintain its integrity due to its primary cross-linked network, resulting in high fracture energy.[282]

The design principle for tough hydrogels via dissipative bond breaking requires a portion of polymer chains in the network to maintain a high stretch limit and other chains to dissipate mechanical energy under the deformation. In a double network hydrogel, the polymer network with high stretch limit is often made by polymer with low cross-linking density, thus has lower modulus, while the component responsible for mechanical dissipation is often more highly cross-linked and stiffer. Sun et al. synthesized a hybrid hydrogel composed of alginate and PAAm.[283] The hydrogel precursor is created by dissolving alginate and acrylamide in deionized water. The PAAm network is UV cross-linked, while the alginate network is cross-linked with an ionic cross-linker, namely a calcium sulfate slurry. The integration of these two types of cross-linking results in a denser and more interconnected network structure. This dual-network system combines the robustness of covalent bonds with the reversible nature of ionic bonds. The stress strain curves of the dual-network hydrogel as well as single network alginate and PAAm hydrogels are plotted in Figure 11A. The toughness of the hydrogel is significantly enhanced by the sacrificial ionic bonds within the alginate network. Under mechanical stress, these ionic bonds can break and then reform, effectively dissipating energy and allowing the hydrogel to withstand large deformations without failing. For a single network hydrogel, the enhancement of toughness can be achieved through the strategic incorporation of multifunctional cross-linkers. The polymer chains spanning between two cross-linkers have a range of different chain lengths. The shorter chains serve as a sacrificial network, preferentially breaking when subjected to strain, thereby dissipating energy. In contrast, longer chains ensure the structural integrity of the material, enabling it to endure extensive elongation. In addition to this length distribution, multifunctional cross-linkers, for example nano-confined domains induced by noncovalent interactions, can also immobilize nearby polymer chains and deform under strain, leading to substantial energy dissipation and resistance to crack propagation. The dynamic and reversible nature of the noncovalent interactions within these domains allows for repeated rupture and reformation during deformation, combining high strength, ductility, and toughness within a single-network architecture.[284] Cai et al. introduced enzymatic hydrolysis lignin into PVA hydrogels, fostering nanophase separation alongside Ag^+ adsorption. The Ag nanoparticle-reinforced PVA hydrogel exhibits a hierarchical structure where Ag nanoparticles create localized high-density cross-linking zones through metal−ligand coordination with lignin. These coordination complexes form a network of reinforcement points that immobilize PVA chains and create nanoscale energy dissipation sites. The resultant hydrogel showed a remarkable toughness of 78.1 MJ/m^3, tensile strength of 13.3 MPa, and a high maximum strain up to 1220%.[285]

The proportion of noncovalent cross-links within a hydrogel network significantly impacts its time-dependent mechanical properties, including viscoelasticity, which is a measure of the time-dependent mechanical performance of materials. Sacrificial noncovalent interactions contribute to viscoelastic behaviors since the physical bond breaking probability is dependent on the deformation rate, thus increasing the noncovalent cross-linking density can result in more viscoelastic hydrogels. For instance, Zhao et al. introduced a physically cross-linked supramolecular-assembled peptides hydrogel coupled to hyaluronan exhibiting tunable viscoelasticity. The viscoelastic properties of the supramolecular peptide-hyaluronan hydrogels stem from β-sheet nanofibers (5−10 nm diameter) forming a physical cross-linking network with hyaluronan. AFM and rheological measurements revealed that the peptide sequence modifications alter the size, branching density, and interconnectivity of these nanofibrils, directly influencing stress relaxation times without significantly changing the overall network stiffness.[286]

4.1.3. Tuning Pore Structure. Uniform aggregation generally decreases the overall porosity or void fraction of hydrogels, leading to a more compact structure. This is attributed to the formation of denser regions within the hydrogel network as polymer chains cluster together.[287] While homogeneously inducing aggregation by adding more physical cross-links may contribute to improved mechanical properties, it may also negatively impact the water content and pore size of hydrogels, resulting in incompatibility with cells.[288] Therefore, controlling the pore structures in hydrogels via noncovalent aggregation stands out as another practical strategy to optimize the mechanical properties of hydrogels for tissue engineering applications. When noncovalent aggregation is spatially confined, aggregation can also take place heterogeneously, resulting in dense polymer aggregation phase coexisting with nonaggregated phases and voids. This results in a nonuniform distribution of pore sizes throughout the material.[289] By manipulating the morphology and size of porous structures, mechanical properties can be tuned without compromising the overall water content.

Stimuli that induce aggregation via phase separation can create porous polymer network from the polymer rich phase. These stimuli include nonsolvents and cosolvents. Duan et al. explores the fabrication of PVA hydrogels with tunable anisotropic mechanical properties using a bidirectional ice templating method.[290] During directional freezing, a second temperature gradient created by a thermal insulating wedge influences the alignment and distribution of the ice crystals,

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Chem. Rev. XXXX, XXX, XXX−XXX

resulting in anisotropic structures with varied degrees of pore alignment. Figure 11B1 and B2 are the SEM images of the cross sections and modulus/ultimate tensile strength of samples in the y direction, which show that as the inclination of the wedge increases from 0 to 40 degrees, the alignment of ice crystals will become more ordered and result in higher stiffness and strength in the direction parallel to the wedge surface. The anisotropic porous structure significantly affects the hydrogel's mechanical properties. The orientation and alignment of the pores, controlled by the bidirectional freezing process, enable the hydrogels to exhibit different mechanical strengths and moduli in various directions. This method enables hydrogels to be made stiffer in one direction compared to another, which is crucial for replicating the mechanical behavior of natural tissues that have inherent anisotropy, such as muscles and tendons.

4.1.4. Inducing Anisotropy. Many biological tissues like tendons and muscles are anisotropic due to the requirement of uniaxial loading for their biological functions.[291] For hydrogels applied in the engineering of these types of tissues, only the mechanical properties along the loading direction are of importance. Therefore, we can specifically optimize the mechanical properties along the loading direction by creating anisotropic microstructures in the hydrogel at the cost of decreasing the mechanical robustness perpendicular to the loading direction. For anisotropic materials, the stiffness will increase along the alignment direction of polymer chains. To model this behavior, a single network polymer matrix can be described using the Gaussian chain model, where the polymer chains are assumed to adopt a random walk coil dimension.[292] The probability of a polymer chain having an end-to-end distance of R can be expressed as

$$G(R) = \frac{1}{(2\pi)^3}\int e^{ikR}\left(\int e^{ikr}\zeta(r)dr\right)^N dk \tag{8}$$

where N is the number of segments in the polymer chain. For chains with a large number of segments (N) and short end-to-end distances, the probability distribution can be approximated as

$$G(R) \approx \left(\frac{3}{2\pi Nl^2}\right)^{3/2} e^{-3R^2/2Nl^2} = \left(\frac{3}{2\pi\langle R^2\rangle}\right)^{3/2} e^{-3R^2/2\langle R^2\rangle} \tag{9}$$

where l is the length of each segment. Whereas for chains with larger end-to-end distances, higher order terms need to be included, so that the expression becomes

$$G(R) = \left(\frac{3}{2\pi Nl^2}\right)^{3/2} e^{-3R^2/2Nl^2}\left[1 - \frac{3}{20N}\left(5 - \frac{10R^2}{Nl^2} + \frac{3R^4}{N^2l^4} + ...\right)\right] \tag{10}$$

Retractive force caused by the change of entropy can be calculated by

$$f = -kT\frac{\partial \ln P(N, R)}{\partial R} \tag{11}$$

For small chain extension scenario,

$$f = \frac{\partial F(N, R)}{\partial R} = -kT\frac{\partial \ln P(\Omega)}{\partial R} = -\frac{3kTR}{R_0^2} \tag{12}$$

For long end-to-end distance R

$$f = \frac{3kT}{l\left[\left(\frac{R}{Nl}\right) + \frac{3}{5}\left(\frac{R}{Nl}\right)^3 + \frac{99}{175}\left(\frac{R}{Nl}\right)^5 + ...\right]} \tag{13}$$

These two equations show that a larger amount of chain stretching will induce larger retractive force. Thus, in hydrogel materials with polymer chain alignment, stress caused by stretching will increase with the degree of chain alignment.

For obtaining anisotropic mechanical properties, ice templating can be adopted to induce chain aggregation into certain aligned morphologies to mimic natural tissues like tendon and cartilage.[290] The anisotropic chain aggregation can also be induced after the gelation using mechanical force for chain alignment. Chen et al. developed a PVA and tannic acid (TA) hydrogel.[262] The solution TA and PVA is cast into molds and subjected to a freezing/thawing cycle to induce physical cross-linking by condensation of precursor solution. Post fabrication, the hydrogels are soaked in a NaCl solution, which influences the physical cross-linking by promoting chain aggregation through a salting-out effect. Upon application of a stretching force, there is significant alignment of the polymer chains. The physical cross-linking through saline soaking and subsequent chain alignment dramatically enhances the hydrogel's mechanical properties. Figure 11C compares the modulus and toughness of samples fabricated with different TA content, with or without stretching and NaCl soaking step. It shows that the addition of TA, chain alignment induced by stretching and salt treatment all contribute to the exceptional strength (up to 750 MPa in aligned PVA-TA threads) and toughness due to the effective alignment of chains and increased cross-linking density.

Chain alignment can also be enhanced by incorporating stiffer fibrous materials into hydrogels. With unidirectional fibers, the properties of the composite material can then be calculated through the volume fraction of fiber and matrix (V_f and V_m respectively), according to the rule of mixtures.

$$\sigma_{c,parallel} = V_f\sigma_f + V_m\sigma_m \tag{14}$$

If it is assumed that the bonding between fibers and the matrix is perfect, and so that the strain in both is the same and equal to that of the composite on applying a longitudinal tensile load.

$$E_{c,parallel} = V_fE_f + V_mE_m \tag{15}$$

$$E_{c,perpendicular} = \frac{E_mE_f}{V_mE_f + V_fE_m} \tag{16}$$

The incorporated fibers are not necessarily unidirectionally aligned, and the fibers can be combined with the matrix by various methods. For hydrogel composites containing fibers with inhomogeneous sizes, shapes, and orientations, their mechanical properties exhibit anisotropy and cannot be well predicted by the rule of mixtures; therefore, it is necessary to employ complex theories in composite structures and micromechanics. Eshelby's equivalence and Mori-Tanaka's mean-field theory are useful in correlating the inhomogeneous microstructures with macroscopic mechanical properties. The average stress and strain fields in the composites can be calculated by considering the interaction between the hydrogel matrix and the fiber inclusions. Probability density functions

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Chem. Rev. XXXX, XXX, XXX−XXX

$p(\theta)$ can be introduced to describe the probability distribution of the fiber orientations.

$$\langle \cdot \rangle = \int_{\pi/2}^{\pi/2} (\cdot) p(\theta) d\theta \tag{17}$$

where $\langle \cdot \rangle$ denotes the orientational average of quantities with an orientational angle θ. For a unidirectional alignment, the probability density function $p(\theta)$ is a Dirac delta function. For transversely isotropic hydrogel/fiber composite, $p(\theta) = \frac{1}{\pi}$. For any other random distribution of fiber orientations, $p(\theta)$ can be experimentally characterized by SEM and Fourier transform.

The toughness of fiber-reinforced hydrogels is often increased through the mechanism of fiber pull-out. This process allows the hydrogel to absorb more energy during deformation, improving its resistance to fracture.

Xing et al. fabricated hydrogel composites using aramid nanofibers (ANFs) to significantly enhance their mechanical properties.[293] The hydrogel composites are created by dispersing ANF pulp in deionized water, which is then mixed with an acrylamide-poly(ethylene glycol) diacrylate hydrogel solution and a water-soluble photoinitiator. During the UV irradiation, the ANFs within the hydrogel undergo photodegradation, which creates reactive sites on their surface. This photodegradation facilitates the formation of new covalent cross-links between the ANF surfaces and the hydrogel matrix. The presence of these aramid nanofibers leads to the formation of a hybrid network, which is further enhanced by additional hydrogen bonding introduced by amide groups on the ANFs. The high-aspect-ratio nanofibers form an interconnected scaffold, providing multiple energy dissipation mechanisms through fiber pull-out and sacrificial hydrogen bond breaking, showing significant improvements in strength, fracture energy, and fatigue threshold—approximately ten times greater than those of the pure hydrogel, as plotted in Figure 11D1 and D2. The modulus is enhanced by about 30 times without significantly compromising the hydrogel's elongation at break.

4.2. Drug Delivery

Hydrogels are well-suited for drug delivery systems targeting the skin, cardiovascular tissues, bones, ocular tissues, and tumors, owing to their distinct physicochemical properties and microstructures, such as high loading capacity, biocompatibility, and controlled degradability.[294,295] A high swelling ratio is essential for efficient drug loading, while a well-regulated deswelling rate is equally important to ensure precise control over the release of therapeutic agents, optimizing treatment effectiveness over time.[296] Covalently cross-linked hydrogels have the limitation of tunability of swelling ratio and swelling rate due to the comparatively stable nature of the covalent bonds. The noncovalent interactions play a pivotal role in the swelling and deswelling during the loading and releasing of drugs. Drugs can be loaded into hydrogels by physical absorption, encapsulation, or through covalent or noncovalent polymer-drug interactions. Drugs can be released by diffusion through the hydrogel matrix, the biodegradation of the hydrogel, or the breakdown of the drug-polymer interactions.[297] By manipulating these interactions, researchers can tune the swelling ratio and swelling rate of the hydrogel, which in turn influences the drug loading and release kinetics of the encapsulated drug.[298]

4.2.1. Selection Criteria for Drug Delivery Applications. *4.2.1.1. Noncovalent Interactions and Selection Criteria.* Drug delivery hydrogels utilize noncovalent interactions that do not affect the effectiveness of the drugs while enabling controlled release over defined timeframes. Hydrogen bonding provides controlled retention and release of polar drugs while maintaining biocompatibility, with tunable strength based on polymer characteristics and environmental conditions. Ionic interactions offer pH-responsive drug retention valuable for site-specific delivery through selective dissociation under specific conditions, while also enhancing residence time at absorption sites.[299] Hydrophobic interactions dramatically improve encapsulation of poorly water-soluble drugs through formation of micellar domains that enhance solubility and control release kinetics.[300] Host−guest interactions using cyclodextrins enable precise control through selective molecular inclusion based on size and polarity complementarity, offering exceptional specificity for targeted applications.[301] In advanced delivery systems, these interactions are often combined, where hydrogen bonds provide matrix stability, ionic interactions enable triggered release, and hydrophobic domains improve loading efficiency for lipophilic compounds.[302]

4.2.1.2. Aggregation Methods and Selection Criteria. Drug delivery applications demand aggregation methods that preserve therapeutic agent stability while enabling precise control over release kinetics. Optimal methods include: pH-responsive aggregation, which creates structures that protect drugs in acidic environments but release contents at neutral pH—essential for oral delivery of acid-labile compounds; temperature-induced phase transition, which enables minimally invasive delivery through solutions that transition to gels at body temperature, conforming to irregular tissue cavities while providing sustained local release;[303] ionotropic gelation, which encapsulates sensitive biologics under exceptionally mild conditions without organic solvents or temperature extremes, preserving the bioactivity of proteins and peptides with >95% retention of function;[304] and controlled phase separation, which creates heterogeneous structures with drug-rich and drug-poor domains that enable biphasic release profiles—initial burst followed by sustained delivery.[305] These methods are commonly used to address requirements in drug delivery applications: pH-responsive techniques enable targeted delivery to specific physiological locations, temperature-responsive systems exhibit both low invasiveness and precise drug localization, ion stimulated approaches preserve the integrity of sensitive biomolecules, and phase separation methods enable more complex drug release profiles to satisfy therapeutic needs.[306]

4.2.2. Tuning Physical Cross-link Density. Higher cross-linking density can lead to reduced swelling due to the denser network structure, while the drug release of hydrogel matrix is significantly influenced by the ratio of mesh size to drug and the strength of the polymer-drug interaction.[307] Temperature, pH or ion responsive hydrogels are particularly useful in drug delivery systems. Temperature-responsive hydrogels are advantageous in drug delivery because they can respond to physiological temperature changes. In diseased tissues like tumors, pH varies significantly, making it a very common stimulus in drug delivery.[308] Ionic-sensitive hydrogels are also useful in drug delivery applications since they can be designed to remain stable in the acidic environment of the stomach but swell and release their contents when exposed to the higher ionic strength in the intestine.[309] A nonswelling ethoxylated polyol thiol−ene hydrogel has been designed for tailorable

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Chem. Rev. XXXX, XXX, XXX−XXX

macromolecule delivery, addressing issues of uncontrolled swelling associated with conventional PEG hydrogels.[310] Hydrophobic drugs are typically encapsulated within the hydrogel matrix through hydrophobic interactions. These interactions help to stabilize the drug within the hydrogel and prevent premature release. The hydrogels begin to swell as the water molecules infiltrate the polymer network. This can lead to a gradual release of drug due to the reduction in hydrophobic interactions because water molecules can interfere with the cohesive forces that hold the hydrophobic drug molecules together. This release rate can be controlled by adjusting the density of hydrophobic domains within the hydrogel.[311]

4.2.3. Tuning Pore Structure. The porous structure of hydrogels significantly impacts their swelling ratio and swelling rate. Larger pores can enhance the swelling ratio, while high pore interconnectivity and more uniform distribution facilitate rapid water infiltration. Moreover, the porous surfaces of hydrogels have higher surface area for water contact, increasing the initial swelling rate.[312,313]

Stimuli that can induce phase separation, such as nonsolvent and solvent, can cause chain aggregation and result in porous structure. Chen et al. developed a super porous poly(acrylamide-*co*-3-sulfopropyl acrylate) hydrogel with interconnected open pores of several hundreds of micrometers. The porous structure is produced using $NaHCO_3$ as foaming agent. This hydrogel can swell to equilibrium size in minutes because of the capillary force that drives water through the open porous structure. It can also achieve high swelling ratio of hundreds of times its dry weight.[314]

4.3. Soft Electronics

Hydrogels are increasingly being explored as soft battery separators due to their unique properties, such as high water content, flexibility, and biocompatibility.[315] A primary requirement for hydrogels in this application is high ion conductivity, which can ensure efficient ion transport between the anode and cathode to support smooth electrochemical reactions. Additionally, the hydrogel must withstand mechanical impact and deformation while maintaining structural integrity to ensure the battery's safety and reliability.[316] Traditional covalently bonded hydrogel materials always face the inevitable conflict between high ionic conductivity and robust mechanical performance. Hydrogels with high ionic conductivity often have a high water content or low cross-linking density, which can weaken their mechanical strength. The incorporation of noncovalent interaction solves this problem ingeniously by inducing aggregated structures with connected pores with dense pore walls.

4.3.1. Selection Criteria for Soft Electronics Applications. *4.3.1.1. Noncovalent Interactions and Selection Criteria.* Hydrogels utilized in soft electronics require interactions that enables a matrix with high ionic conductivity while providing mechanical durability and environmental stability. Hydrogen bonding, ionic interactions and hydrophobic interactions are some commonly utilized noncovalent interactions in hydrogel materials for sensors, bioelectric interfaces, soft circuits and battery separators.[317−319] These interactions enable the porous yet mechanically robust networks by enabling the dense pore walls. Certain hydrogels with ionic domains exhibit continuous ionic networks that facilitate ion hopping or diffusion, further improving the overall ionic mobility. Some kosmotropic ions have the effect of enhancing the noncovalent interactions between polymer chains while decreasing the freezing point of the hydrogel, improving environmental stability.

4.3.1.2. Aggregation Methods and Selection Criteria. Soft electronic applications require aggregation methods that maintain continuous ion pathways while providing mechanical robustness. Key approaches include: freeze−thaw cycling, which creates heterogeneous structures with densely aggregated polymer domains separated by water-rich channels—ideal for combining mechanical strength with high ionic conductivity (10−30 mS/cm);[320] salting-out method, which induces controlled polymer aggregation while simultaneously improving conductivity;[321] controlled phase separation, which generates bicontinuous structures with polymer-rich phases forming the mechanical framework and polymer-poor phases creating interconnected channels for ion transport;[322] and cononsolvency-induced aggregation, which creates multiscale porous networks through the paradoxical solubility behavior of polymers in mixed solvents.[323] These methods address the specific challenges of soft electronics: freeze−thaw techniques create the heterogeneous microstructures necessary for balancing mechanical and electrical properties, salting-out approaches enable the environmental stability required for outdoor applications, phase separation creates the optimized ion transport pathways essential for high conductivity, and cononsolvency produces the multiscale structures that combine mechanical robustness with electrical performance—collectively enabling the fabrication of sophisticated ionic devices that maintain functionality under mechanical deformation and environmental fluctuations.

4.3.2. Tuning Pore Structure. The porous structure of hydrogels is critical for mass transport. An optimal pore size and distribution are necessary to allow for the free movement of ions while preventing the passage of larger, unwanted particles or dendrites that could cause short circuits.[324] The interconnected pore network should be designed to provide low resistance pathways for ion transport while maintaining robust mechanical performance. To meet these requirements, an advanced separator/electrolyte that possesses adequate ionic conductivity for battery functionality and resilience to mechanical impacts is essential. This can be achieved by leveraging the cononsolvency and "salting-out" effects in the synthesis of a PVA hydrogel.[325] The cononsolvency effect induces phase separation that leads to the formation of open-cell porous structures, while the "salting-out" effect promotes polymer chain aggregation and crystallites formation that densify the polymer network. The low tortuosity of the interconnected pores enhances ion diffusion, while the high concentration of physical cross-linking improves structural integrity. The resultant hydrogel exhibits high ionic conductivity (49.8 mS/cm) as well as high tensile strength (15.6 MPa). These properties enable the hydrogel to support stable battery operation of over 30,000 cycles and endure extreme mechanical stress, such as being hit by a hammer.

4.4. Sensors and Actuators

Hydrogels can function as sensors by responding to various environmental stimulus such as temperature,[326] pH,[327] humidity,[328] light,[329,330] electric field[331] and specific chemical or biological agents. These stimuli-responsive hydrogels undergo shape, optical or other types of changes that can be easily detected and measured. Hydrogels that can convert these environmental stimuli into mechanical motion can be used as

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Chem. Rev. XXXX, XXX, XXX−XXX

actuators.[332,333] The swelling and shrinking behavior of hydrogels in response to stimuli can be harnessed to create actuators that perform work or generate movement. The key challenges for these applications are high sensitivity, response specificity, response rate and reversibility.[334] Conventional covalently cross-linked hydrogels have the limitation of low reconfigurability, poor fatigue resistance, slow response rate and restricted stimuli responsiveness. These limitations can be overcome by the incorporation of noncovalent interactions, which can quickly respond to a wide range of stimuli, form and break in a reversible way, and enhance mechanical performance.

4.4.1. Selection Criteria for Sensors and Actuators Applications. *4.4.1.1. Noncovalent Interactions and Selection Criteria.* Sensors and actuators require rapidly reversible noncovalent interactions with fast response times, high cycling stability, and strong stimulus-response coupling. Hydrogen bonding provides temperature sensitivity with rapid bond formation/disruption kinetics, creating sharp transition thresholds that translate small temperature changes into significant mechanical responses.[335] Hydrophobic interactions is often utilized in such applications since they generate substantial contractile forces upon heating above transition temperatures.[336] Ionic interactions produce dramatic and selective changes in swelling ratio when specific ions are present, enabling highly specific chemical sensors with excellent selectivity and sensitivity.[337] Chemical sensors often use host−guest interactions due to the highly specific molecular recognition systems with tunable binding kinetics. Photoresponsive interactions enable light-controlled actuation through isomerization or ionization, allowing remote and noncontact actuation.[338]

4.4.1.2. Aggregation Methods and Selection Criteria. Sensors and actuators require aggregation methods that produce structures with rapid, reversible responses to specific stimuli. Essential approaches include: temperature-induced phase transitions, which create materials that respond to subtle thermal changes through reversible polymer chain aggregation, enabling both sensing and actuation with response times under 1 s;[339] light-triggered aggregation, which provides unprecedented spatial and temporal control through incorporation of photosensitive molecules that undergo isomerization, ionization, or cleaving upon specific wavelength exposure;[340] and pH-responsive techniques, which generate structures that swell/contract in response to protonation/deprotonation around specific pK_a values, creating highly selective ion sensors with detection limits in ppb range.[341] These methods directly address the functional requirements of sensing and actuation devices: temperature-responsive approaches create the thermally sensitive materials necessary for temperature detection or thermal actuation, light-triggered systems enable the spatial precision required for complex patterned responses, pH-methods provide the chemical specificity essential for ion detection, and ionic approaches facilitate the electrical control needed for device integration—collectively enabling the fabrication of sophisticated responsive systems that translate environmental stimuli into measurable signals or mechanical work with high fidelity and reproducibility.[342]

4.4.2. Reversible Interactions. The stimuli responsiveness of hydrogels is often based on reversible noncovalent interactions. The reversible nature of these interactions allows the hydrogel to undergo significant changes in its physical state without permanent alteration of its chemical structure. For hydrogen bonding, increased temperature provides thermal energy that can disrupt hydrogen bonds;[343] pH changes alter the ionization state of functional groups involved in hydrogen bonding;[344] the presence of solvents that compete for hydrogen bonding can disrupt these interactions.[345] For ionic interactions, ion concentration changes in the environment can screen or enhance the electrostatic forces, affecting the strength of ionic interactions; alterations in pH can change the ionization state of the functional groups, thereby influencing ionic interactions;[346] the polarity of the solvent can affect the strength of ionic interactions by altering the solubility of the ions.[347] Hydrophobic interactions are driven by the thermodynamic preference to reduce the system's free energy by minimizing the interface between nonpolar groups and the surrounding water.[348] Changes in temperature can affect the entropy and enthalpy of the system;[349] the introduction of nonpolar solvents can enhance hydrophobic interactions by providing a more favorable environment for nonpolar groups to aggregate;[350] the presence of surfactants can disrupt hydrophobic interactions by reducing the surface tension between nonpolar groups and water.[351] For van der Waals forces, increased temperature can promote thermal motion that overcome van der Waals forces;[352] changes in pressure can influence the distance between molecules or atoms, affecting the strength of van der Waals forces;[353] the presence of other molecules that can induce dipoles or interact with existing dipoles that modulate van der Waals interactions.[354] The removal of such perturbations can allow these interactions to recover.

The choice of stimuli that best suits the application of hydrogel-based sensors and actuators depends largely on the specific functional requirements of the devices. For hydrogel actuators, which are designed to perform mechanical work in response to external stimuli, the change in ion concentration and variations in temperature are among the most commonly utilized triggers.[355] Light can also be effectively used to power hydrogel actuators, particularly when photothermal materials are incorporated into the hydrogel matrix.[356] These stimuli effectively induce volumetric changes in the hydrogel, leading to its expansion, contraction, or shape changing, which can be harnessed to achieve motion control or manipulation of objects. For hydrogel-based sensors, the range of detectable stimuli is broader. These sensors can be designed to respond to changes in ion concentration, pH, temperature, and light, among other stimuli.[357] Qin et al. introduced a hydrogel-based interferometer that exhibits adaptive coloration as an effective chemical sensor.[358] The hydrogel interferometer consists of a single hydrogel thin film covalently bonded to a reflective substrate. The hydrogel's response to chemical stimuli involves uniform dimensional changes across the entire film, where hydrogen bonding networks are disrupted by external stimuli, such as the presence of volatile vapors or changes in humidity. This thickness variation alters the path length light travels inside of the material, leading to a change in observed color after interference. This hydrogel interferometer, inspired by biological adaptive color systems, offers a simplified yet effective approach to chemical sensing.

When the volumetric change caused by reversible interactions is large enough and can generate mechanical motion, these hydrogels can be used as actuators. For example, Zhao et al. incorporated gold nanoparticles as a photothermal agent into asymmetric cylindrical PNIPAM hydrogel pillar, which undergoes a large volume shrinkage when heated above its

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Chem. Rev. XXXX, XXX, XXX−XXX

LCST.[359] Hydrophobic interaction is induced by high temperatures above LCST, thus promoting chain aggregation and resulting in a reduction in swelling ratio of the material. As a result, the hydrogel pillar can respond to a green laser by bending toward the incident light due to photothermal heating and perform oscillatory motion via a built-in feedback loop for the self-shadowing mechanism. Furthermore, the hierarchical structure demonstrates the possibility of accelerating the response rate, which will be utilized for real-world applications like grippers, walkers, valves, etc.[360]

4.5. Wound Dressing

In wound dressing applications, hydrogels are esteemed for their multifaceted benefits that encompass various stages of the wound healing process, such as hemostasis, inflammation, proliferation, and tissue remodeling.[361] These polymeric materials excel in providing a moist environment that not only promotes faster healing but also acts as a protective barrier against microbial invasion and environmental contaminants. Apart from these functionalities, hydrogels materials applied in wound dressing are also required to be adhesive to the wounded tissues to ensure stable attachment and conformability during motion.[362] This is particularly challenging for covalently cross-linked hydrogels, which often have lower adhesion to tissues due to the lack of bonding sites. Hydrogels with noncovalent interactions, on the other hand, often exhibit reversible and dynamic adhesion properties, allowing them to adhere and detach without causing damage to the tissue.

4.5.1. Selection Criteria for Wound Dressing Applications. *4.5.1.1. Noncovalent Interactions and Selection Criteria.* Hydrogels for wound dressing applications require noncovalent interactions that support healing, provide appropriate adhesion and effectively manage exudate. Ionic interactions form adaptable structures that control fluid absorption through reversible ion exchange, responding dynamically to wound conditions.[363] Hydrogen bonding networks maintain optimal moisture balance through dynamic water binding.[364] Hydrophobic interactions create selective adhesion to skin while minimizing adhesion to vulnerable wound beds.[365] Hydrophobic domains also form essential bacterial barriers. van der Waals forces help establish initial contact between the hydrogel and wounds. These weak but numerous attractions collectively contribute to the overall adhesion, especially at the microscale where the hydrogel can conform to tissue topography. Multiple interaction types working synergistically create responsive dressings that adapt to the changing wound environment throughout healing.[366]

4.5.1.2. Aggregation Methods and Selection Criteria. Wound dressing applications require biocompatible aggregation methods that produce structures balancing adhesion to tissue with exudate management and antimicrobial properties. Effective approaches include: ionic cross-linking, which creates dressings that respond dynamically to wound exudate through formation of gel structures upon contact with wound fluid; temperature-responsive aggregation, which enables precise filling of wound cavities through in situ gelation at skin temperature, particularly valuable for irregular or tunneling wounds[367] and controlled phase separation, which generates porous structure with high absorbency and mechanical integrity through polymer-rich and polymer-poor domains that have superior fluid absorbing ability while maintaining bacterial barriers.[368] These methods address specific wound care challenges: ionic strategies enable adaptive absorption to accommodate fluctuating exudate levels, temperature-responsive systems enhance precision in application for complex wounds and phase separation produces structural heterogeneity to support both exudate control and bacterial protection. Together, these methods offer advanced wound management solutions that foster optimal healing conditions while meeting the practical demands of clinical use.[369]

4.5.2. Bond Formation. Noncovalent interactions, such as hydrogen bonding, hydrophobic interactions and van der Waals forces, contribute to adhesive property of hydrogels.[370] Formation of noncovalent bonds between polymer chains and the functional groups on biological tissues, such as hydroxyl groups, carboxyl groups, amino groups, sulfhydryl groups, and amide groups, facilitates adhesion of these hydrogels. Stimuli such as pH, ion concentration, temperature, and light can be used to control the strength of adhesion of hydrogels to wounded tissues. Adjusting the pH can shift the functional groups between protonated and deprotonated states, altering the strength of hydrogen bonding between the hydrogel and the tissue. For ionic interactions, pH changes can alter the charge distribution on the hydrogel and tissue surfaces, affecting adhesion strength. Variations in ionic strength can influence ionic interactions within the hydrogel and between hydrogel and the tissue, further modulating adhesion. Temperature changes can affect the strength of hydrophobic interactions within the hydrogel, leading to alterations in its adhesive properties to hydrophobic regions on tissues. Additionally, light-responsive hydrogels that incorporate photothermal materials can modify their adhesion properties when exposed to light that turns into heat, providing a versatile tool for controlling adhesion in wound dressings. Cui et al. developed a novel type of organic−inorganic hybrid hydrogel for instant wound dressing.[371] This material is fabricated by polymerization of *N*-acryloyl 2-glycine with a natural mineral. The high mechanical properties are attributed to hydrogen bonding, ionic cross-linking and the interaction between polymer chains and mineral nanoparticles. The combines effect of carboxyl functional groups and the nanoparticles achieves a adhesion strength with soft tissues of 105 kPa.

5. CONCLUSION AND OUTLOOK

Noncovalent interactions play a central role in facilitating hydrogel aggregation by controlling the structural organization, properties, and functionalities of these materials. Throughout this review, we have systematically explored how different types of noncovalent interactions—including hydrogen bonding, ionic interactions, hydrophobic effects, and $\pi-\pi$ stacking—govern the formation of hydrogel networks and modulate key characteristics such as mechanical strength, stimuli-responsiveness, and swelling behavior. By analyzing the inherent properties of these interactions and the fabrication approaches they enable, we have shown that strategic selection and tuning of noncovalent interactions offer a powerful route for optimizing hydrogel performance across diverse applications. However, several critical challenges remain before the full potential of noncovalent interaction-induced hydrogels can be realized. These include achieving long-term structural stability under dynamic environmental conditions, enhancing the reproducibility of physically aggregated hydrogel networks, and integrating slow, interaction-driven fabrication processes with rapid material shaping techniques commonly used in advanced manufacturing.

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Chem. Rev. XXXX, XXX, XXX−XXX

Maintaining the structural integrity of hydrogels in dynamic or harsh conditions—such as fluctuating pH, temperature, or ionic strength—is particularly challenging due to the inherently reversible nature of noncovalent interactions. To address this, one effective strategy is to construct systems composed of complementary interaction mechanisms that respond robustly across different environmental conditions. For instance, hydrogels that combine ionic cross-linking with hydrophobic domains can achieve greater environmental tolerance and long-term mechanical resilience. Another successful approach is the use of double-network hydrogels, in which a covalently cross-linked permanent network provides overall stability, while a physically cross-linked network dissipates energy and contributes to adaptive behavior. This dual-function design allows the hydrogel to maintain structural coherence while exhibiting tunable or responsive behavior, which is particularly useful in biomedical and soft robotics applications.

Another major challenge is the difficulty in reliably reproducing the final microstructure and properties of noncovalent hydrogels, due to the sensitivity of these interactions to subtle environmental fluctuations and processing conditions. Addressing this issue first requires a fundamental understanding of how specific stimuli—such as temperature, solvent polarity, and ionic strength—induce or modulate different types of noncovalent interactions. By identifying the key thermodynamic and kinetic parameters that control the aggregation pathway, such as mixing rate, concentration, and diffusion times, researchers can gain predictive control over the resulting gel architecture and interaction strength. In addition, process optimization techniques, including real-time monitoring through turbidity, rheological tracking, or spectroscopy, can help ensure reproducibility during fabrication. Templated or seeded assembly processes, in which nucleating structures direct the organization of supramolecular networks, also show great promise for improving structural uniformity.

A further challenge lies in the mismatch between the slow kinetics of many noncovalent aggregation methods and the high-speed requirements of modern shaping technologies, such as 3D printing, microfluidic molding, and injection casting. Overcoming this incompatibility will likely require the adoption of multistage fabrication workflows. In such approaches, the hydrogel precursor can be rapidly shaped using a printable or moldable formulation that undergoes fast gelation, followed by post-treatment to induce a second network or to enhance properties through more time-consuming aggregation methods. For example, a hydrogel can be printed via a shear-thinning ink and then strengthened through ionic soaking, freeze–thaw cycling, or environmental conditioning. In cases where noncovalent interactions are required for the initial shaping phase itself, the design of materials must accommodate rapid, in situ physical cross-linking. Co-engineering of equipment and materials is also a promising path forward; for instance, integrating a cooling platform into an extrusion-based 3D printer enables freeze-casting effects to occur concurrently with shaping, enabling directional aggregation during the printing process. Similarly, solvent exchange systems or temperature-controlled nozzles can initiate noncovalent assembly directly during extrusion.

Beyond these physical and chemical strategies, integrating data-driven and computational approaches may further advance the field. Machine learning models trained on formulation–property data sets can predict optimal interaction schemes for target performance profiles, while molecular simulations can offer mechanistic insights into interaction dynamics and pathway selection. High-throughput experimental platforms, capable of testing multiple conditions in parallel, can accelerate the identification of robust and reproducible processing parameters.

Apart from these general challenges and opportunities, there are some open issues remaining in different application domains.

Tissue Engineering: Noncovalent interactions largely govern the structural integrity and mechanical properties of hydrogels for tissue engineering. However, challenge still remains in achieving long-term stability while maintaining biocompatibility. Future research should focus on fine-tuning dynamic noncovalent interactions to create hydrogels that provide adaptive mechanical properties and controlled degradation profiles. A deeper understanding of how multiscale aggregation mechanisms impact tissue regeneration will further enhance their applicability.

Drug Delivery: Noncovalent interactions play a crucial role in encapsulating and releasing drugs. While ionic interactions and hydrogen bonding enable precise control over drug loading and release kinetics, challenges persist in achieving high-loading capacities without compromising structural stability. The development of hydrogels with tunable noncovalent networks that respond to specific biological stimuli (e.g., pH, enzymes, or temperature) could significantly improve targeted and sustained drug delivery systems.

Soft Electronics: Hydrogels in soft electronics rely on noncovalent interactions for flexibility, ionic conductivity and low-temperature tolerance. However, a major limitation is maintaining long-term electrical performance under repeated mechanical deformation. Addressing this requires designing hydrogels with robust reversible noncovalent cross-links that balance self-healing and conductivity, particularly in extreme environments.

Sensors and Actuators: For hydrogels to function effectively in sensors and actuators, noncovalent interactions must enable rapid and reversible response mechanisms while achieving high loading in some cases. Future research should explore hybrid noncovalent cross-linking strategies that leverage multiple interactions simultaneously to achieve faster actuation, prolonged operational stability and high actuation force.

Wound Dressing: The adhesion and mechanical resilience of wound dressings are directly influenced by noncovalent bonding mechanisms such as hydrogen bonding and ionic interactions. Although recent advancements have improved wet adhesion strength, challenges remain in designing materials with simultaneous strong adhesion, biocompatibility, and antimicrobial properties. Future efforts should explore novel biomimetic strategies to harness multiple noncovalent forces for improved adhesion in dynamic biological environments.

In conclusion, the future development of noncovalently aggregated hydrogels hinges on our ability to understand, manipulate, and stabilize their dynamic interactions across multiple length and time scales. By combining mechanistic knowledge with innovative fabrication strategies and leveraging computational tools, researchers can develop next-generation hydrogels with finely tuned structure–property–function relationships. These materials will not only offer superior mechanical and functional performance but also align with the growing demands of scalable, adaptive, and programmable soft

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Chem. Rev. XXXX, XXX, XXX−XXX

materials for applications in medicine, energy, robotics, and beyond.

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Chem. Rev. XXXX, XXX, XXX−XXX

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ABBREVIATIONS

PVA = Poly(vinyl alcohol)
PEG = Polyethylene glycol
PAAm = Poly(acrylamide)
PNIPAM = Poly(*N*-isopropylacrylamide)
PANI = Polyaniline
PPV = Polyphenylenevinylene
PEDOT = Poly(3,4-ethylenedioxythiophene)
PAA = Poly(acrylic acid)
PMAA = Poly(methacrylic acid)
PAMPS = Poly(2-acrylamido-2-methylpropanesulfonic acid)
PHEA = Poly(2-hydroxyethyl acrylate)
PVAc = Poly(vinyl acetate)
PVP = Poly(*N*-vinylpyrrolidone)
PU = Polyurethane
PPO = Poly(propylene oxide)
PTh = Polythiophene
PU = Polyurea
PTNVE/DMA = Poly(N1,N1,N2,N2-tetramethyl-N1-(naphthalen-2-ylmethyl)-N2-(4-vinylbenzyl)ethane-1,2-diaminium-*co*-N,N-dimethylacrylamide
PSSA = Poly(4-styrenesulfonic acid)
PMAm = Poly(methacrylamide)
DMSO = Dimethyl sulfoxide
CD = Cyclodextrin
a-CD = α-Cyclodextrin
β-CD = β-Cyclodextrin
Ad = Adamantyl
n-Bu = *n*-Butyl
t-Bu = *tert*-Butyl
SDS = Sodium dodecyl sulfate
NaSS = Sodium p-styrenesulfonate
MPTC = 3-(methacryloylamino)propyl-trimethylammonium chloride
OP-4-AC = Octylphenol polyoxyethylene acrylate
DMF = Dimethylformamide
AM = Acrylamide
HA-gels = Hydrophobic association hydrogels
CB[8] = Cucurbit[8]uril
AAm = Acrylamide
MBAA = N,N'-methylenebis(acrylamide)
DMF = N,N-dimethylformamide
PA = Peptide amphiphile
Alg = Alginate
C18 = Stearyl methacrylate
C22 = Dococyl acrylate
HAP = Hydroxyapatite
GelMA = Gelatin methacryloyl
HEA = Hydroxyethyl acrylate
NBNAGA = N'-(2-nitrobenzyl)-*N*-acryloyl glycinamide
BIS = N,N'-methylene bis-acrylamide
DVS = Divinyl sulfone
TA = Tannic acid
MOF = Metal−organic framework
AgNP = Silver nanoparticle
RSF = Regenerated silk fibroin
ANF = Aramid nanofiber
MNP = Magnetic nanoparticle
HFMOS = Hydrogel with Fiberboard-and-Mortar Ordered Structure
ANF = Aramid nanofibers
SR = Slide-ring
LCST = Lower critical solution temperature
UCST = Upper critical solution temperature
DLCA = Diffusion-limited cluster−cluster aggregation
RLCA = Reaction-limited cluster−cluster aggregation
NIPS = Nonsolvent induced phase separation
RAFT = Reversible addition−fragmentation chain transfer
UTS = Ultimate tensile strength

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Chem. Rev. XXXX, XXX, XXX−XXX