



Review

# Tough Hydrogels with Different Toughening Mechanisms and Applications

Zhengyu Xu <sup>1</sup>, Yanru Chen <sup>1</sup>, Yi Cao <sup>1,2,\*</sup> and Bin Xue <sup>1,2,\*</sup>

<sup>1</sup> Collaborative Innovation Center of Advanced Microstructures, National Laboratory of Solid State Microstructure, Department of Physics, Nanjing University, Nanjing 210093, China; dz1922031@smail.nju.edu.cn (Z.X.); mg21220197@smail.nju.edu.cn (Y.C.)

<sup>2</sup> Jinan Microecological Biomedicine Shandong Laboratory, Jinan 250000, China

\* Correspondence: caoyi@nju.edu.cn (Y.C.); xuebinnju@nju.edu.cn (B.X.)

**Abstract:** Load-bearing biological tissues, such as cartilage and muscles, exhibit several crucial properties, including high elasticity, strength, and recoverability. These characteristics enable these tissues to endure significant mechanical stresses and swiftly recover after deformation, contributing to their exceptional durability and functionality. In contrast, while hydrogels are highly biocompatible and hold promise as synthetic biomaterials, their inherent network structure often limits their ability to simultaneously possess a diverse range of superior mechanical properties. As a result, the applications of hydrogels are significantly constrained. This article delves into the design mechanisms and mechanical properties of various tough hydrogels and investigates their applications in tissue engineering, flexible electronics, and other fields. The objective is to provide insights into the fabrication and application of hydrogels with combined high strength, stretchability, toughness, and fast recovery as well as their future development directions and challenges.

**Keywords:** hydrogels; high toughness; sacrificial bonds; hierarchical architecture; network topology; force-triggered length release; tissue engineering; flexible electronics



**Citation:** Xu, Z.; Chen, Y.; Cao, Y.; Xue, B. Tough Hydrogels with Different Toughening Mechanisms and Applications. *Int. J. Mol. Sci.* **2024**, *25*, 2675. <https://doi.org/10.3390/ijms25052675>

Academic Editor: Ylenia Zambito

Received: 7 February 2024

Revised: 20 February 2024

Accepted: 24 February 2024

Published: 26 February 2024



**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

A hydrogel is a type of polymer network with a three-dimensional structure that contains hydrophilic groups and can swell in water, typically with a water content ranging from 50% to 99.9%. Hydrogels are characterized by good biocompatibility, the ability to regulate crosslinked networks, responsiveness to external stimuli, and molecular permeability [1]. They find wide-ranging applications in tissue engineering [2–4], adhesive materials [5,6], drug delivery [7,8], artificial muscles [9], different types of sensors [10–12], soft robots [13,14], brain-computer interfaces [15], and other fields. Currently, most traditional hydrogels are soft and brittle, with mechanical properties such as fracture stress, fracture strain, and fracture toughness far lower than natural materials. This low toughness is attributed to the uneven topology of their crosslinked networks, which lack effective energy dissipation mechanisms to prevent crack propagation and stress concentration. Consequently, when subjected to external forces, the stress in the hydrogel quickly concentrates on structural defects or weak crosslinking points, leading to rapid crack expansion and eventual failure, severely limiting their practical applications [16–18]. Additionally, there is often a trade-off between strength and toughness in hydrogels, as these properties are mutually exclusive [19].

Designing hydrogels with high toughness is key to addressing the challenges and has become a hot research topic. Tough hydrogels exhibit excellent ductility, high toughness, pressure resistance, and self-healing ability [20,21]. The density and dynamic characteristics of crosslinking points [22,23], the uniformity of the network structure [24], and the density and flexibility of the polymer chain [25,26], among other factors, all affect the mechanical strength of hydrogels. In addition, the special design of the hydrogel network structure is

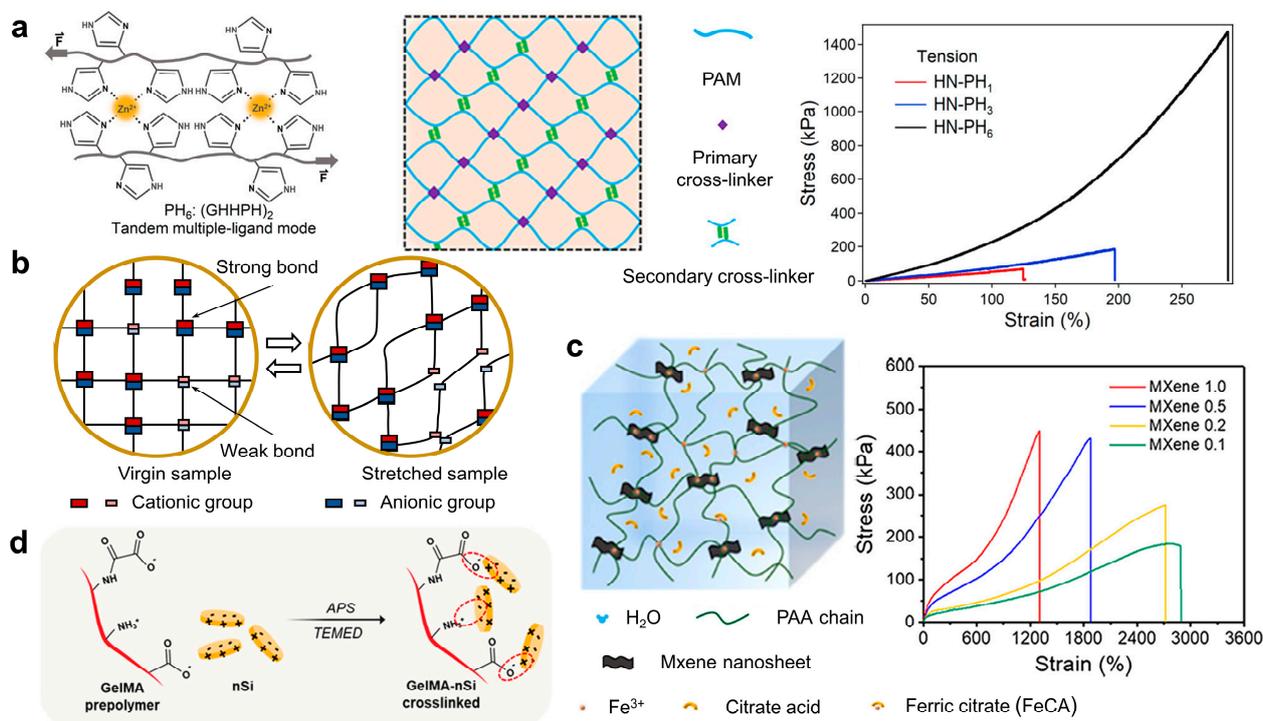
also crucial for improving the mechanical properties of hydrogels. Common methods to enhance the toughness of hydrogels include introducing sacrificial units to dissipate energy, such as double-network hydrogels and some single-network hydrogels [27–30]; increasing the crosslink density by enhancing the functionality of single crosslink points, as seen in nanocomposite hydrogels [31,32]; improving the uniformity of the hydrogel crosslinked network [33]; and introducing “molecular sliding mechanisms” or strong dynamic interaction systems, such as slide-ring hydrogels and some single-network hydrogels [34,35]. These different design strategies can also be combined to fabricate composite hydrogels with excellent mechanical properties, which have been studied and discussed in depth by researchers before [36–38]. Compared with previous reviews, this review comprehensively discusses the design principles and toughening mechanisms of tough hydrogels, as well as classifies them according to their characteristics. This review also introduces the mechanical properties of various tough hydrogels and their applications in tissue engineering, 3D printing, flexible electronic devices, and so on. Furthermore, we also discussed the remaining challenges of tough hydrogels and look forward to future development directions and challenges.

## 2. Strategies and Properties of Tough Hydrogels

### 2.1. Toughening Hydrogel with Sacrificial Bonds

The most commonly used method to enhance the toughness of hydrogels is through sacrificial bonds, which include single-network hydrogels and double-network hydrogels. Single-network hydrogels have a simple structure and are earlier developed hydrogel network systems with limited tensile properties and toughness [39,40]. To improve their tensile properties and toughness, a non-covalent crosslinking network structure can be introduced, resulting in a hydrogel with two different crosslinking mechanisms [41–44]. The covalent crosslinking points provide stability to the mechanical structure and matrix modulus, while the reversible secondary crosslinking points on the polymer chain segments or side chains act as the main energy dissipation mechanism to enhance hydrogel toughness. For instance, Cao et al. developed strong, tough, and fast-recovery hydrogels by incorporating a specially designed peptide-metal complex as the physical crosslinker, as shown in Figure 1a. The decapeptide used in their study contained two tandem zinc-binding motifs and had high thermodynamic stability, strong binding strength, and a rapid binding rate with  $Zn^{2+}$ . This peptide-metal complex enabled fast binding and unbinding kinetics. Moreover, the presence of multiple ligands within each binding site and the cooperative arrangement of binding sites enhanced the stability and strength of the hydrogels. As a result, the engineered hybrid network hydrogels, containing the peptide-zinc complex, exhibited a break stress of approximately 3.0 MPa, a toughness of about  $4.0 \text{ MJ m}^{-3}$ , and fast recovery within seconds [45]. Additionally, Gong et al. introduced a hydrogel with ionic bonds of varying strengths, formed through the electrostatic interaction between two oppositely charged polyelectrolytes (3-(methacrylamido)propyl-trimethylammonium chloride (MPTC) and sodium p-styrenesulfonate (NaSS)). As shown in Figure 1b, the strong bonds act as permanent crosslinking points, providing sufficient matrix elasticity, while the weak bonds reversibly dissociate and dissipate energy. This hydrogel exhibits a fracture energy of  $4 \text{ kJ m}^{-2}$  [46]. Furthermore, Sheiko et al. designed a N,N-dimethylacrylamide and methacrylic acid couple (DMAA-co-MAAc) copolymer hydrogel utilizing the collaborative crosslinking of hydrogen bonds and covalent bonds. It exhibits a Young's modulus of up to 28 MPa and a toughness of up to  $93 \text{ kJ m}^{-2}$ . This hydrogel also shows fatigue resistance and restorability, demonstrating the feasibility and advantages of combining reversible hydrogen bonding and covalent bonding in preparing stretchable and tough hydrogels [47]. Single-network hydrogels with high toughness can also be created solely through physical interactions, including ionic interactions, hydrogen bonds, hydrophobic interactions, metal coordination interactions, protein-specific interactions, and so on [48–52]. Strong physical interactions ensure the physical properties of hydrogels, while reversible dynamic physical interactions provide self-healing properties to hydrogels [53]. For instance, Sherman et al.

utilized the host–guest interaction between acrylamide and cucurbituril as a reversible sacrificial bond to dissipate energy and prepared a supramolecular hydrogel with a tensile strain of 107 times. This hydrogel also exhibits significant self-healing properties and conductivity at room temperature [54].



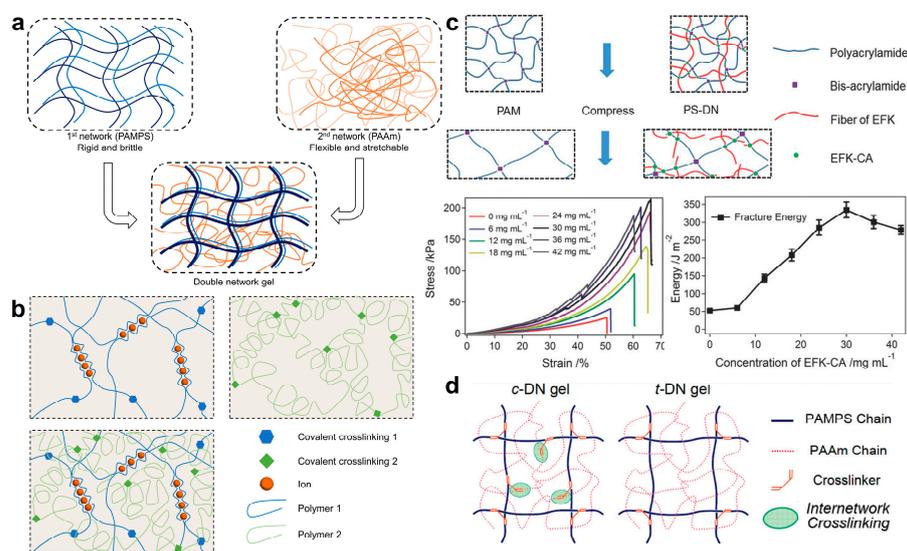
**Figure 1.** Schematic of single-network hydrogels toughening with sacrificial bonds. (a) Molecular engineering of metal coordination interactions for strong, tough, and fast-recovery hydrogels. Reprinted with permission from Ref. [45]. 2020, American Association for the Advancement of Science. Schematic illustration of metal ion coordination complexes formed by two metal chelation sites in tandem (PH<sub>6</sub>); schematic illustration of the network structure of HN-PH<sub>6</sub> hydrogels and uniaxial stress-strain curves under tension. (b) Schematic of the structure of physically crosslinked hydrogel composed of polyampholytes. During the deformation of hydrogels, the strong ionic bonds act as permanent crosslinkers, similar to covalent bonds, while weak ionic bonds serve as reversible sacrificial crosslinkers, adapted from Ref. [46]. (c) Schematic of the highly stretchable and tough nanocomposite physical hydrogels, which contain MXene nanosheets that served as multifunctional crosslinkers and effective stress transfer centers, as well as the stress–strain curves. Reprinted with permission from Ref. [55]. 2022, American Chemical Society. (d) The components involved in the chemical crosslinking of the mechanically tough nanocomposite hydrogel. The electrostatic interaction between GelMA and nSi is highlighted. Reprinted with permission from Ref. [56]. 2023, American Chemical Society.

Nanocomposite hydrogels are systems formed by using nanomaterials as high-functionality crosslinking points to connect multiple polymer chains [57,58]. Nanomaterials encompass inorganic salt particles, carbon-based nanomaterials, metal nanomaterials, polymer colloids, and so on [59,60]. The surface of nanomaterials used as crosslinking points in nanocomposite hydrogels is easier to be modified and connected with a variety of polymer chains, compared with that of traditional crosslinking networks. When stretched, a small amount of polymer chains in these hydrogels will break and consume energy without affecting the elongation of the main chain. As a result, nanocomposite hydrogels exhibit excellent tensile properties and high toughness. For example, Li et al. designed a polyacrylamide/calcium hydroxide (Ca(OH)<sub>2</sub>) nano-spherulites (PAM/CNS) nanocomposite gel with extremely strong stretchability

and ultra-high toughness based on the polyacrylamide and low-concentration, small-sized calcium hydroxide nanospherulites [61]. Some nanocomposite hydrogels use nanowires or nanotubes as crosslinking points, such as carbon nanotubes, assembled nanowires, and so on [62,63]. These hydrogels not only exhibit excellent stretchability and high toughness but also possess photoelectric or other special properties. They can be used in applications such as drivers, conductive tapes, biosensors, artificial skin, and other fields. The solubility or stability of carbon-based materials can be enhanced by modifying polar groups or stabilizers on the surface, including amino groups, carboxyl groups, proteins, pyrene molecules, and so on. Subsequently, the modified carbon-based materials can be connected with polymer chains [64]. For example, Liu et al. synthesized a nanocomposite hydrogel based on the hydrogen bonding of nanotubes and poly-acryloyl-6-amino caproic acid, which has excellent stretchability and self-healing properties [65]. In addition, Ma et al. constructed injectable antibacterial conductive cryogels based on carbon nanotube (CNT) and glycidyl methacrylate functionalized quaternized chitosan. These gels exhibit robust mechanical strength, rapid blood-triggered shape recovery, and absorption speed, as well as high blood uptake capacity, indicating their great potential for use in noncompressible hemorrhage hemostasis dressing and wound healing applications [66]. Nanosheets or nanoribbons are utilized as crosslinking points in two-dimensional nanocomposite hydrogels, including clay nanosheets, graphene sheets, and so on [5]. In 2002, Haraguchi et al. peeled the synthesized clay into nanosheets and then modified hydrophilic monomers on the surface. Subsequently, they prepared novel nanocomposite hydrogels with a unique organic–inorganic clay network structure through a free radical polymerization [67]. They further studied the properties of nanocomposite hydrogels using clay nanosheets as crosslinking points and optimized the tensile properties and toughness by preparing polymer brushes or adsorbing polymer chains on the surface of the clay sheets. Additionally, Lu et al. reduced graphene oxide into conductive graphene using polydopamine and then formed PDA-pGO-PAM hydrogels based on the covalent and physical interactions of polyacrylamide and conductive graphene. This hydrogel exhibits extremely high tensile properties, excellent electrical conductivity, ductility, high toughness, viscosity, self-healing properties, biocompatibility, and more. Consequently, it can be used in implantable bioelectronic devices and other fields [68]. In another study, as shown in Figure 1c, Xie et al. proposed highly stretchable high-toughness nanocomposite physical hydrogels based on a multibond network design rationale, which contain 2D  $Ti_3C_2T_x$  MXene nanosheets served as multifunctional crosslinkers and effective stress transfer centers. These conductive MXene and numerous ions enable hydrogels to have high toughness, superior conductivity, strain sensitivity, and self-healing performance, suggesting great potential for use in intelligent flexible electronics [55]. As depicted in Figure 1d, Arghya et al. constructed a mechanically tough nanocomposite hydrogel for pharmaceutical drug delivery by exploiting the electrostatic interaction between nanosilicates (nSi) and gelatin methacrylate (GelMA). Notably, this hydrogel is prepared at subzero temperatures and possesses macroporous structures, rendering it suitable for cell infiltration [56]. In addition, vitrimers containing reversible covalent bonds can also enhance the mechanical properties of hydrogels [69,70]. For example, Cedric developed a type of vitrimer gel based on transesterification through the epoxy ring-opening reaction with carboxylic acids of functionalized poly (ethylene glycol) (PEG) and triglycidyl ether crosslinkers. It exhibits a good maximum strain (300%), high conductivity, and full recovery, allowing it to be used as a strain sensor, soft electrode, and ionic cable [71].

A double-network hydrogel consists of two interpenetrating polymer networks that can be chemically or physically crosslinked and are independent of each other. This method is widely used to prepare highly tough hydrogels by designing a unique energy dissipation mechanism in the crosslinking network of double-network hydrogels [72–74]. A fully chemically crosslinked double-network hydrogel, also known as a covalent double-

network hydrogel, consists of two polymer networks connected by chemical bonds that are independent of each other. Osada et al. first proposed a covalent double-network hydrogel through two-step continuous free radical polymerization in 2003, in which the primary network is a dense rigid network and the secondary network is a loose flexible network. The rigid polyelectrolyte network poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) was first polymerized and then the primary network was immersed in an aqueous solution containing neutral monomers. Then, the loose secondary high molecular weight polyacrylamide covalent network PAAm was polymerized in the swollen primary network. Finally, a PAMPS-PAAm double-network hydrogel containing intertwined loose long chains and dense short chains was obtained, as shown in Figure 2a [75]. The primary polyelectrolyte network undergoes extreme swelling, causing it to break into small cluster structures that serve as sliding crosslinking points in the secondary loose network. The rupture of covalent bonds in the short chains consumes a significant amount of energy, providing the hydrogel with mechanical strength. Meanwhile, the loose secondary network structure gradually straightens from its curled and entangled state, contributing to the ductility of the hydrogel. The synergistic effect of these two different covalent networks enables the hydrogel to dissipate energy under large strains, resulting in high toughness and excellent tensile properties. These properties are much better than those of traditional single polyelectrolyte hydrogels or polyacrylamide hydrogels [73]. Lu et al. fabricated an NPs-pectin-polyacrylic acid adhesive hydrogel using Ag-Lignin nanoparticles (NPs) to initiate dynamic redox catechol chemistry. The presence of silver lignin nanoparticles establishes a sustained reductive-oxidative environment within the hydrogel network. Continuously generated catechol groups enable the hydrogel to preserve its adhesive properties, while also demonstrating exceptional resistance to stretching and high toughness. Additionally, this hydrogel exhibits favorable cell compatibility and shows high antibacterial activity, thereby holding potential for application in tissue engineering [76].



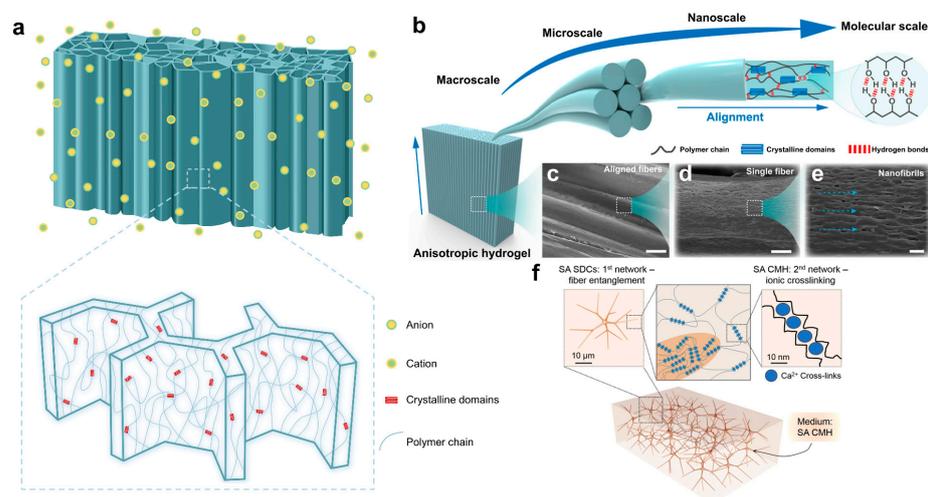
**Figure 2.** Schematic of double-network hydrogels toughening with sacrificial bonds. (a) PAMPS-PAAm covalent double-network hydrogels, adapted from Ref. [75]. (b) An alginate-polyacrylamide hybrid gel based on the ionic crosslinking of alginate and the covalent crosslinking of acrylamide, adapted from Ref. [21]. (c) A polymer-supramolecular polymer double-network hydrogel based on the combination of a polyacrylamide covalently crosslinked network and a self-assembled polypeptide fiber supramolecular network EFK, as well as the compression-fracture curves and fracture energies at different EFK-CA (EFK peptide with a cinnamic acid) concentrations. Reprinted with permission from Ref. [77]. 2016, John Wiley and Sons. (d) Truly independent double-network gels and double-network gels with two networks interconnected. Reprinted with permission from Ref. [78]. 2009, American Chemical Society.

Covalent double-network hydrogels typically dissipate energy through the irreversible breakage of the first-level network. However, this toughening mechanism renders them unable to recover from initial damage and lacking in anti-fatigue properties, thus impacting their potential applications in biological scaffolds, cartilage repair, and so on. To address these limitations, researchers have focused on introducing dynamic physical crosslinked networks to replace the first-level “sacrificial network” in covalent double-network hydrogels. These dynamic physical networks utilize various mechanisms such as ionic pairing [21,49,79], hydrophobic interactions [80], hydrogen bonding [81], coordination interactions [82–84], and host–guest interactions. These double-network hydrogels are characterized by their high toughness, exceptional stretch resistance, fatigue resistance, self-healing ability, and other properties [85]. For example, Suo et al. proposed an alginate-polyacrylamide hybrid gel based on the ionic crosslinking of alginate and the covalent crosslinking of acrylamide, as shown in Figure 2b. These two crosslinked networks are covalently linked through amino groups and carboxyl groups [21]. The ionic crosslinked network is capable of dissipating energy through reversible dissociation, while the covalent network of the hydrogel inhibits crack expansion, thereby ensuring the high toughness of the hydrogel. This study provides a model for exploring the mechanisms of hydrogel deformation and energy dissipation. Additionally, inspired by the unique polymer-supramolecular polymer double-network (PS-DN) architecture found in natural articular cartilage [86], Wang et al. developed a PS-DN hydrogel based on the combination of a polyacrylamide covalently crosslinked network and a self-assembled polypeptide fiber supramolecular network EFK. This hydrogel dissipates energy by employing the EFK polypeptide fiber network as a “sacrificial” bond during compression and has high toughness, as illustrated in Figure 2c. Upon release of the force load, the polypeptides rapidly reassemble, endowing the hydrogel with rapid self-repair capabilities. This makes it a potential candidate for high-toughness materials in the regeneration of load-bearing tissues such as cartilage [77]. In most cases, a physical crosslinked network is dynamic and easy to break under strains, and the overall mechanical properties of physical crosslinked double-network hydrogels are still limited. However, Cao et al. have reported that tuning the network structures can improve the mechanical properties of these hydrogels, potentially offering new insights into combining high mechanical strength and fast recovery in physically crosslinked double-network hydrogels [87]. In addition, Gong et al. synthesized a series of physically crosslinked double-network hydrogels based on amphiphilic triblock copolymers, which contain strong hydrophobic domains and sacrificial dynamic bonds of hydrogen bonds. These hydrogels are stiff, and tough, and feature improved self-healing and self-recovery abilities [88]. Another approach to constructing hybrid double-network hydrogels involves introducing microcrystalline structures into covalent single-network hydrogels [89,90]. For example, Suo et al. proposed a crystallized polyvinyl alcohol/polyacrylamide (PVA-PAAm) gel utilizing a dry annealing method, which can dissipate energy through the reversible disassembly of the high-density polyvinyl alcohol microcrystalline physical network. As a result, this hydrogel possesses high mechanical strength and toughness. In addition, the polyacrylamide covalent network provides matrix elasticity for this hydrogel [90]. Another research focus is on developing biomimetic double-network hydrogels based on the characteristics of biopolymers in nature. For example, Chen et al. synthesized highly mechanical and recoverable double-network hydrogels through a one-pot synthesis approach. The agar molecules can form a double helix structure at room temperature and assemble into a thick helical bundle physical crosslinked network due to heat sensitivity. They will break into small cluster structures to dissipate energy when the hydrogels are stretched. Then, the agar molecules can return to their original state at high temperatures and enable the hydrogel to possess self-healing properties. The fracture strain can reach 20 times the original length [91]. As shown in Figure 2d, Gong et al. have also contributed to the field by demonstrating the anomalous high strength some double-network gels can attain when the second network is polymerized without any crosslinkers. This is due to the interconnection between the two networks through

covalent bonds, and they named these kinds of double-network gels c-DN gels. They also synthesized truly independent double-network gels, which do not have covalent bonds between the first and the second networks, and named them t-DN gels. They demonstrated that t-DN gels cannot be toughened by the uncrosslinked second network [78].

## 2.2. Toughening Hydrogel with Hierarchical Architecture

Natural structural materials often possess excellent mechanical properties resulting from their complex hierarchical assembly across multiple length scales. Therefore, it is possible and challenging to develop hydrogels with multi-level special network architectures, which can significantly enhance their mechanical properties for various applications, such as bioengineering [92–101]. He et al. introduced a strategy to create a multi-length-scale hierarchical hydrogel architecture utilizing a freezing-assisted salting-out treatment. The produced poly(vinyl alcohol) hydrogels exhibit excellent ultimate stress, high strain levels, and high toughness, benefiting from the highly anisotropic structures. These structures consist of micrometer-scale honeycomb-like pore walls, which are composed of interconnected nanofibril meshes, as depicted in Figure 3a. The properties of these hydrogels are even superior to those of natural tendons with the same water content. These strategies can also be applied to other polymers [102]. For example, He et al. also constructed a stretchable conducting tough hydrogel through an ice-templated, low-temperature polymerization (ITLP) strategy. This hydrogel has a hierarchical dendritic microstructure with mitigated nanoaggregation and exhibits an 83-fold enhancement in conductivity and a 29-fold increase in toughness. Thanks to its excellent mechanical and electrical properties, this hydrogel can be used as a wearable supercapacitor and has potential applications as a high-performance soft electronic material in the fields of healthcare and robotics [103]. Zhai et al. also fabricated a strong and tough hydrogel with architected multiscale hierarchical structures through a freeze-casting-related strategy. The entangled crosslinked strong polyvinyl alcohol chains with chain-connecting ionic bonds, the hydrogen bond- and coordination bond-enhanced fibers with nanocrystalline domains, and the microscale anisotropic honeycomb-structured fiber walls and matrix constitute the multi-level hierarchical structures of the hydrogel and obviously enhance the mechanical properties of it [104].



**Figure 3.** Schematic of high-toughness hydrogels toughening with hierarchical architecture. (a) A multi-length-scale hierarchical hydrogel prepared through freezing-assisted salting-out treatment, adapted from Ref. [102]. (b–e) Schematic illustration of anisotropic hydrogels with multiscale hierarchical architectures from macroscale to molecular scale and multiscale magnified SEM images showing the preferentially aligned fiber structures. The scale bars for (c–e) are 100, 10, and 2 μm, respectively. Reprinted with permission from Ref. [105]. 2024, Springer Nature. (f) Schematic of the hierarchical interactions between the colloidal and molecular alginate networks in a class of self-reinforced homocomposite hydrogels. Reprinted with permission from Ref. [106]. 2021, Springer Nature.

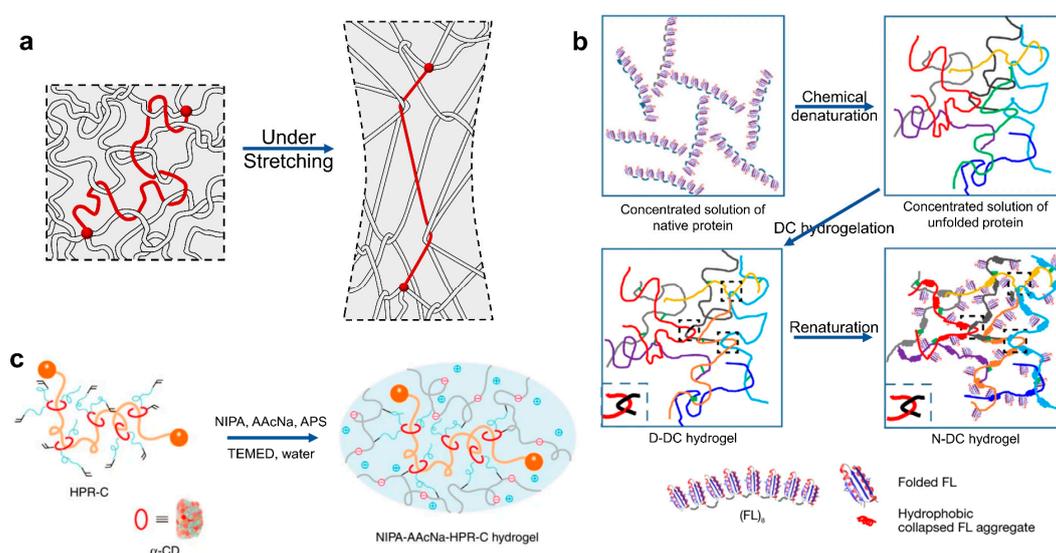
Additionally, Lin et al. proposed a simple yet versatile method to construct hierarchically structured hydrogels through the flow-induced alignment of nanofibrils, as shown in Figure 3b–e. The obtained anisotropic hydrogels exhibit a highly aligned fibrous configuration and structural densification, leading to desired mechanical properties and damage-tolerant architectures. The strength can achieve  $14 \pm 1$  MPa, and the toughness can achieve  $154 \pm 13$  MJ m<sup>-3</sup>. These hydrogels also hold potential for water purification applications due to the ultra-fast and unidirectional water transport ability [105]. Furthermore, Zhu et al. developed a flexible, high-strength hydrogel with a fiberboard-and-mortar hierarchically ordered structure based on ultralong hydroxyapatite nanowires and polyacrylic acid, inspired by natural biological soft tissues. This hydrogel has a high water content, dense structures, and excellent mechanical properties similar to human cartilage, resulting in a huge potential for water purification, pollution treatment, biomedicine, nanofluidic devices, high-performance structural materials, and other applications [107]. As shown in Figure 3f, Velev et al. reported on a class of self-reinforced homocomposite hydrogels composed of sodium alginate interpenetrating networks of multiscale hierarchy. The storage modulus and Young's modulus of these hydrogels are both enhanced by the colloidal network of hierarchically branched alginate soft dendritic colloids. They can even accomplish the efficient extrusion 3D printing of these hydrogels by balancing the ratio of the precursors [106]. Furthermore, Jeon et al. developed a method to prepare highly anisotropic hydrogels with programmable oriented polymer structures and excellent mechanical properties based on a novel welding technique for stretched cellulose hydrogel films. The anisotropic tough multilayer hydrogels obtained through this method can have different oriented hierarchies, as well as splendid mechanical properties (Young's modulus of ~140 MPa, tensile strength of ~47 MPa). This work opens a new window for designing novel hydrogel materials utilized in engineering and biomedical applications [108].

### 2.3. Toughening Hydrogel with Network Topology

Constructing a uniformly dispersed network system or introducing mechanisms such as molecular entanglement [109] and molecular sliding into the network can significantly improve the mechanical properties of the hydrogels. For instance, Tetra-PEG hydrogel is formed by crosslinking four-armed polyethylene glycol modified with two different functional groups at the ends. It has been demonstrated to possess an extremely uniform network structure, possibly similar to the diamond structure, which significantly enhances its mechanical properties [33,110–112]. Wang et al. proposed chemically crosslinked microsphere composite hydrogels based on core-shell polymer microspheres formed by poly(butyl methacrylate-co-allylamine) (PBMA) with polyacrylamide (PAAm) chains chemically grafted onto their surfaces. The flexibility of the PBMA chains and the hydrogen bonds between the amide groups of the grafted polymer chains results in the reversible deformation of microspheres, providing an additional energy-dissipating mechanism for tough hydrogels. The good compatibility between the microspheres and the matrix polymer chains allows the hydrogel network structure to disperse uniformly, which is the main mechanism of toughening. In addition, hydrogen bonding between grafted polymer chains and reversible deformation of microspheres can also dissipate energy during the stretching process of this hydrogel [113]. Haraguchi et al. prepared Tetra-poly(ethylene glycol)-based nanocomposite hydrogels by in situ polymerization of two different four-armed macromonomers in the presence of clay in aqueous media. This hydrogel has high transparency, high elongation (900~1000%), and high tensile strength, which are approximately 2–4 times those of the corresponding original Tetra-PEG hydrogels [114]. Michelle et al. utilized electrospun gelatin nanofibres to produce aligned hydrogel networks, which are similar to the collagen network in natural tissues. This unique structure effectively resists crack expansion in the hydrogel and toughens it, making it suitable for various biomedical applications [115].

Suo et al. studied the effects of polymer entanglements on fracture, fatigue, and friction. They synthesized polymer hydrogels in which entanglements greatly outnumbered crosslinks. Dense entanglements allow tension in the polymer chain to be transferred to many other chains,

and the sparse crosslinked structures prevent the polymer chains from unraveling, as shown in Figure 4a. Thus, the hydrogels prepared by this method exhibit high toughness, strength, fatigue resistance, low hysteresis, low friction, and high wear resistance [116]. Gong et al. studied the effect of the molecular weight of the second network components on the entangled regions and proved that the entanglement between the second network component plays an important role in the toughening mechanism of double-network hydrogels [117]. In addition, Huo et al. prepared tough and recoverable nanostructured hydrogels through polymerization-induced self-assembly. The hydrophilic chains in its network structure are highly entangled and act as sliding links. The tension can be transferred to the micelle crosslinkers during the deformation process of the hydrogel, thereby dissipating energy through the reversible deformation and irreversible separation of the polymer chains and achieving toughening of the hydrogel [118]. Li et al. reported highly stiff and tough protein-based hydrogels constructed by introducing chain entanglements into the hydrogel network made of folded elastomeric proteins, as shown in Figure 4b. The exhibited mechanical properties are close to those of cartilage, and this hydrogel was proven to be useful in osteochondral defect repair [119].



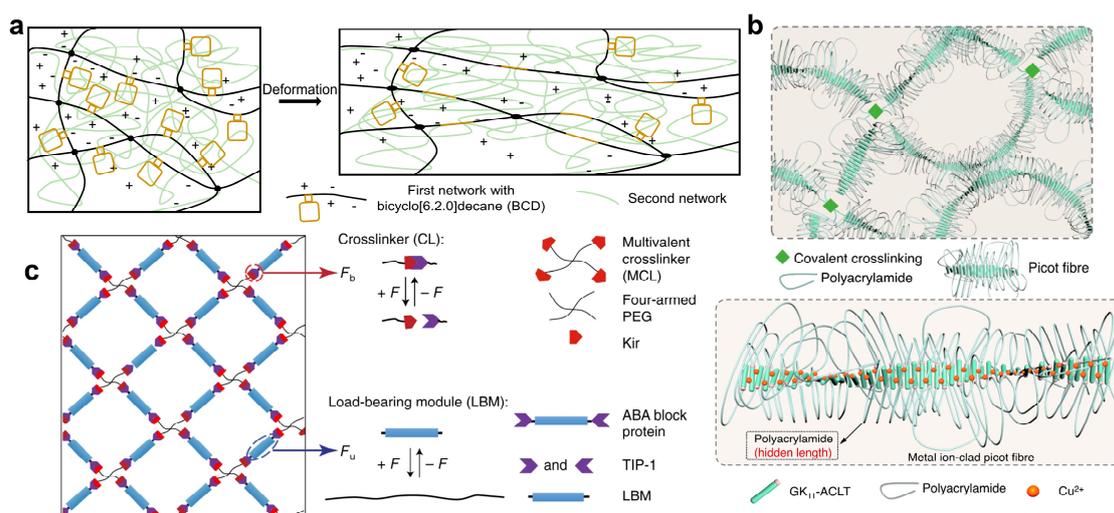
**Figure 4.** Schematic of high-toughness hydrogels toughening with network topology. (a) Schematic of tough hydrogels in which entanglements greatly outnumber crosslinks, adapted from Ref. [116]. (b) Schematics of the preparation of a denatured denatured-crosslinking hydrogel and a native denatured-crosslinking hydrogel. Reprinted with permission from Ref. [119]. 2023, Springer Nature. (c) A NIPA-AAcNa-HPR-C hydrogel containing slip ring structures. Reprinted with permission from Ref. [35]. 2014, Springer Nature.

Slide-ring hydrogels are composed of necklace-shaped macromolecule topological materials, which can be likened to a pulley that can slide randomly on a knotted chain. There are organized molecules at the end of the chain to prevent the pulley from falling off, so slide-ring hydrogels have strong tensile properties. Common cyclic molecules used include polyrotaxanes, catecholamine rings, and others, which are chemically modified to serve as sliding crosslinking points. The unique “sliding mechanism” of slide-ring hydrogels enables them to exhibit significantly different mechanical properties from traditional hydrogels, leading to a wide range of potential applications. For example, Yukikazu et al. used a polyrotaxane derivative composed of  $\alpha$ -cyclodextrin and polyethylene glycol as a crosslinking point and polymerized it with a heat-sensitive N-isopropylacrylamide monomer, as shown in Figure 4c. They introduced ionic groups to promote the dispersion of slip-ring molecules in the system and constructed a NIPA-AAcNa-HPR-C hydrogel with slip-ring structures. It has strong tensile properties similar to soft rubber and can be used for rapid response thermosensitive and pH-sensitive materials [35]. Ichiro et al. demonstrated a novel procedure for synthesizing an aldehyde-containing polyrotaxane (PR $\beta$ CD1), which is composed of  $\beta$ -cyclodextrin ( $\beta$ CD)

monoaldehyde and polypropylene glycol. They also synthesized atelocollagen threads with enhanced mechanical properties by using PR $\beta$ CD1 as a crosslinker (Col-PR $\beta$ CD1) [120]. Moreover, Ito et al. proposed polyethylene glycol hydrogels crosslinked with moderate fractions of polymers that form sliding rings. These hydrogels exhibit high toughness and rapid recovery, owing to the rapid and reversible strain-induced crystallization facilitated by the parallel orientation of the chains when stretched [121].

#### 2.4. Toughening Hydrogel with Force-Triggered Length Release

Introducing force-triggered length release into the crosslinked network offers several benefits, including enhanced stress resistance, energy dissipation under large strains, and reversibility of deformation of the network [122–124]. This mechanism of toughening hydrogels is both innovative and effective. For instance, Craig et al. proposed a polymer network in which the constituent chains can be extended through force-coupling reactions when the chains reach their breaking point. This reactive chain extension only takes place when resistance to fracture is required, as shown in Figure 5a. As a result, the hydrogels exhibit significant toughening, achieving a 40% to 50% further extension through the unfolding of force-coupling structures under high strains, as well as double tearing energy [125]. Cao et al. presented novel types of hydrogels comprised of hierarchical structures of picot fibers, which were made of copper-bound self-assembling peptide strands with a zipped flexible hidden length, as shown in Figure 5b. The picots can efficiently dissipate energy and release the hidden length by rupturing strong inter-peptide interactions without affecting the network connectivity of the hydrogels. Consequently, the obtained hydrogels exhibit an extraordinary combination of high mechanical strength (fracture stress  $\sim 4.1$  MPa), as well as ultrahigh toughness (fracture energy  $\sim 25.3$  kJ m $^{-2}$ ). Furthermore, the reformation of individual picot fibers occurs locally and independently, which ensures the rapid recovery of the hydrogels. This innovative design approach opens up new possibilities for advanced material applications [126]. Fei et al. constructed a super-tough polyacrylamide/iota-carrageenan double-network hydrogel with incorporated bacterial cellulose microclusters. This remarkable hydrogel can withstand tensile stress exceeding 200 kPa, possesses a high toughness of approximately 2000 kJ m $^{-3}$ , and achieves 27 times tensile strain. These exceptional mechanical properties are attributed to the intermolecular hydrogen bonds, the topological interlock, and the hidden length within the polyacrylamide regions [127].



**Figure 5.** Schematic of high-toughness hydrogels toughening with force-triggered length release. (a) A double-network hydrogel with force-coupling structures, adapted from Ref. [125]. (b) A novel hydrogel comprised of hierarchical structures of picot fibers. Reprinted with permission from Ref. [126]. 2023, Springer Nature. (c) Schematic of a protein hydrogel with crosslinkers and folded proteins served as load-bearing modules. Reprinted with permission from Ref. [128]. 2018, Springer Nature.

Zheng et al. utilized 3D printing to create macroscopic super tough hydrogels featuring titin-like domains. When these hydrogels are stretched, the relatively thin and weak gel fibers break first, utilizing their hidden length to effectively delay the failure of the main structure. This mimics the toughening principle of titin and significantly enhances the tensile properties of the hydrogel [129]. Yang et al. proposed a hydrogel with high toughness, rapid self-healing abilities, dynamic adhesive properties, and strain hardening abilities by incorporating rigid tannic acid-coated cellulose nanocrystals into the polyvinyl alcohol-borax dynamic network. The flexible polyvinyl alcohol chains wrapped on the rigid cellulose nanocrystals can be stretched and release a significant hidden length when the hydrogel deforms. At the same time, there are dynamic hydrogen bonds between the tannic surface and the entangled polyvinyl alcohol chains. These two mechanisms synergistically toughen the hydrogel [130]. Babaahmadi et al. developed fully physically crosslinked double-network hydrogels, comprised of the robust agar biopolymer first network and the resilient polyvinyl alcohol second network. By employing cyclic freezing and thawing methods, they created a folded microcrystalline structure within the polyvinyl alcohol network, which unfolds as the hydrogel is stretched, thereby releasing the hidden length and toughening the hydrogel. This double-network hydrogel introducing a folded microcrystalline structure has multiple energy dissipation mechanisms, a high modulus of 2200 kPa, and a high toughness of 2111 kJ m<sup>-3</sup> and can self-heal quickly [131]. Furthermore, introducing folded protein structures into hydrogel crosslinked networks is another approach to incorporate force-triggered length release. For example, Cao et al. demonstrated self-healable muscle-mimicking hydrogels that can significantly dissipate energy through protein unfolding, serving as load-bearing modules regulated by force, as shown in Figure 5c [128].

### 3. Applications of Tough Hydrogels

Hydrogels hold great promise in the biomedical field due to their high water content and excellent biocompatibility. However, traditional hydrogels often suffer from weak mechanical properties, limited functionalities, and a lack of self-healing capabilities, which restricts their applications. By designing complex functional structures within the hydrogel network, it is possible to imbue hydrogels with properties such as super stretch resistance, self-healing, high toughness, environmental sensitivity, conductivity, and so on. Then they can be widely used in tissue engineering, flexible electronic devices, and other biomedical fields, including biological scaffolds, drug delivery, load-bearing 3D printing biomaterials, wearable sensors, bioadhesive materials, and so on.

#### 3.1. Tissue Engineering

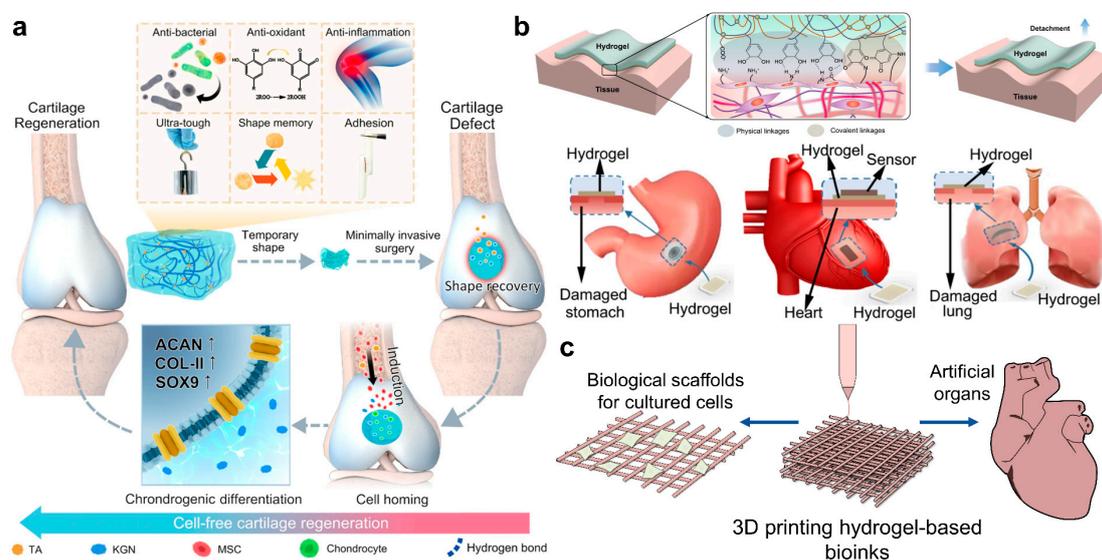
Tissue engineering is a multidisciplinary field focused on developing technologies that provide repair and replacement of damaged tissues and organs by studying factors such as cells, scaffold materials, and growth information [2]. Scaffold materials promote tissue regeneration by providing cells with a chemical environment and mechanical support. Tough hydrogels are expected to be used as a carrier for drug delivery or be used as a biological scaffold for cell culture in applications such as bone repair, cartilage repair, and cardiovascular tissue regeneration, especially after being special functionalized or 3D printed [57,132–140]. For example, Gong et al. introduced natural neutral polyelectrolytes into biopolymer-based tough double-network hydrogels by modifying them in polydimethylacrylamide crosslinked networks. The hydrogel's mechanical strength and toughness are comparable to conventional double-network hydrogels. Meanwhile, it has excellent biocompatibility, and the cell experiments proved that this hydrogel can enhance the adhesion of human coronary artery endothelial cells (HCAECs) and promote cell proliferation, making it a promising candidate for tissue engineering applications, particularly in cardiovascular tissue repair [141]. Wear-resistant double-network hydrogels can be used as cell-free scaffolds for cartilage repair [142]. However, they face challenges in adhering tightly to the joint defect due to the strong water storage capacity. For example,

Tan et al. developed a super-tough hydrogel that can be anchored to cartilage tissue via a dual-bonded approach by using chondroitin sulfate. The hydrogel implant stability with cartilage tissue is improved, and this hydrogel is favorable for chondrocyte attachment, offering the potential for rapid and effective repair of cartilage defects and long-term preservation of joint functionality [143]. In another study, Chen et al. proposed a multiple hydrogen-bond crosslinked hydrogel loaded with tannic acid and Kartogenin through a polyaddition reaction. As shown in Figure 6a, this hydrogel features ultra-durable mechanical properties, adequate adhesiveness with cartilage tissues, anti-inflammation, antibacterial capabilities, antioxidant, and fast shape memory properties, which endows the hydrogel with the potential for minimally invasive surgery. Importantly, the sequential release of tannic acid and Kartogenin can recruit the migration of bone marrow mesenchymal stem cells into the hydrogels and induce chondrocyte differentiation, thus leading to cartilage regeneration *in vivo*. This work may provide a promising solution for advancing cartilage regeneration [144].

In addition, hydrogels have potential applications as artificial bionic tissues for tissue replacement, tissue repair, and other fields if their mechanical properties are excellent enough, such as being very stiff and tough [119,145–147]. For instance, Li et al. designed a significantly stiffened protein-based hydrogel through chain entanglements, which exhibited high toughness, stiffness, fast recovery, and ultrahigh compressive strength. This hydrogel has been demonstrated for its application in cartilage regeneration [119]. Inspired by catechol chemistry discovered in mussel foot proteins, Cao et al. developed a high-toughness covalent hydrogel that can adhere to tissue surfaces through both physical and covalent interactions, as shown in Figure 6b. They have also successfully demonstrated that this hydrogel can be applied to stop bleeding in wounds in different tissues, including the stomach, heart, lungs, and so on [148]. David et al. developed a family of degradable tough adhesive hydrogels by incorporating covalently networked degradable crosslinkers and hydrolyzable ionically crosslinked main-chain polymers. These hydrogels have high fracture energies ( $>6 \text{ kJ m}^{-2}$ ), excellent adhesion energies ( $>1000 \text{ J m}^{-2}$ ), and good biocompatibility [149]. Kim et al. proposed a strong, stiff, and adhesive triple-network anisotropic hydrogel that can mimic a bone-adhering tendon. This anisotropic hydrogel is constructed based on the combination of imidazole-containing polyaspartamide and energy-dissipative alginate–polyacrylamide double-network, including ionic crosslinking interactions and covalent crosslinking interactions. It exhibits anisotropic, high tensile modulus and strength while maintaining high bone adhesion without chemical modification of the bone surface, benefiting from the secondary crosslinking after linearly stretched, similar to the nature of bone-adhering tendons [150]. In addition, Grunlan et al. demonstrated a double-network hydrogel composed of an anionic poly(2-acrylamido-2-methylpropanesulfonic acid) first network and a poly(N-isopropylacrylamide-co-acrylamide) second network. It exhibits similar compressive strength, modulus, and hydration with healthy cartilage, along with a lower coefficient of friction. Therefore, this hydrogel becomes an ideal candidate for synthetic cartilage grafts for chondral defect repair [151]. He et al. reported a soft somatosensitive actuating material composed of conductive photothermal responsive covalent hydrogel, synthesized through an ice-templated ultraviolet-cryo-polymerization technique. It has ultra-high conductivity, high stretchability, and quick response because of the dense conductive network and highly porous microstructure, which makes it a promising candidate for muscle-like materials [152].

Programmatic 3D printing of tough hydrogels with designing complex shapes, structures, and orientation-related properties may also make them be used as biological scaffolds for cultured cells, effectively reduce graft dislocation in medical treatment, better simulate the natural tissue environment, or be used as artificial tissues and organs in tissue engineering, as shown in Figure 6c [134,153–161]. These printable tough hydrogels were typically designed to demonstrate properties such as light-responsive fast curing for applications like stereolithography (SLA) 3D printing and shearing-thinning for processes such as extrusion printing. The strategies of sacrificial bonds were usually utilized to toughen

hydrogels in 3D printing, including nanocomposite hydrogel, double-crosslinked hydrogel, and double-network hydrogel. For example, Liu et al. developed a nanocomposite hydrogel bioink consisting of a hydrogen-bonded monomer N-acryloyl glycinamide and nanoclay. This bioink can be 3D printed into high-strength composite scaffolds with excellent mechanical properties and swelling stability. The sustained release of intrinsic  $Mg^{2+}$  and  $Si^{4+}$  can effectively promote the repair of tibial bones in living mice [134]. In addition, Dai et al. proposed a stable, high strength, and 3D printable novel double crosslinked alginate hydrogel with enhanced mechanical properties and prolonged stability of up to 30 days in medium. This hydrogel holds promise for applications in cartilage defect repair and provides a possible approach for other tissue engineering and regeneration medicine [160]. Parker et al. designed a hydrogel ink containing prefabricated gelatin fibers, which can be used to print 3D organ-level scaffolds that recapitulate the intra- and intercellular organization of the heart [161]. These studies showcase the extensive possibilities of tough hydrogels in 3D printing technologies, opening up exciting prospects in the field of tissue engineering and regenerative medicine.

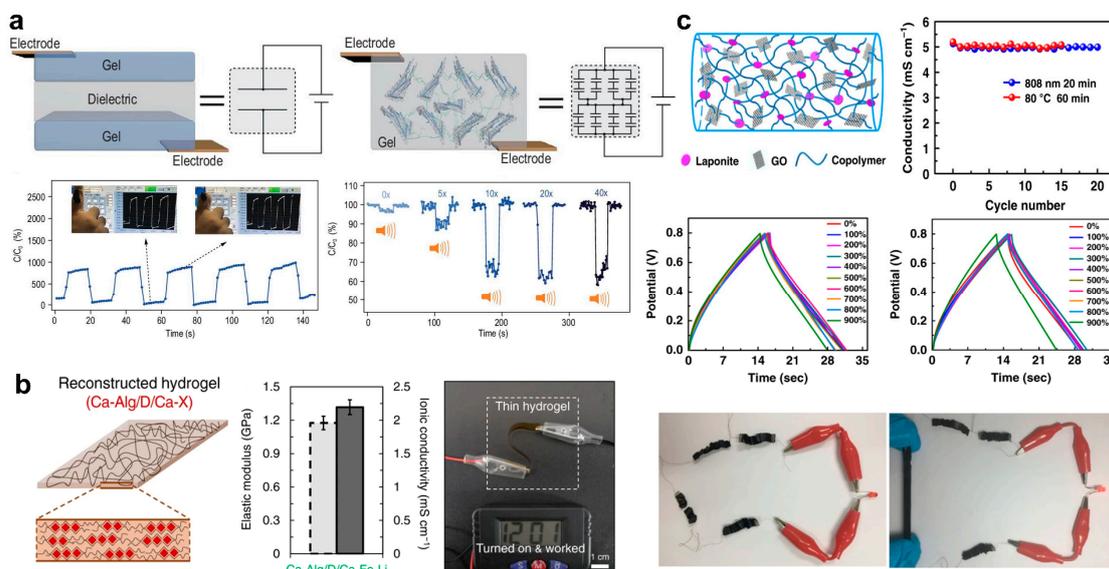


**Figure 6.** Applications of different high-toughness hydrogels in tissue engineering. (a) A multiple hydrogen-bond crosslinked hydrogel loaded with tannic acid and Kartogenin through polyaddition reaction, which can be used in cartilage regeneration in vivo. Reprinted with permission from Ref. [144]. 2023, Springer Nature. (b) Schematics of the adhesion mechanism and bioadhesion applications of a high-toughness hydrogel. Reprinted with permission from Ref. [148]. 2021, Springer Nature. (c) Schematics of 3D printing hydrogel bioink applied to cell culture scaffolds and artificial organs.

### 3.2. Flexible Electronics

Stretchable tough hydrogels have the potential to be designed into various types of sensors when special structures that can respond to external environmental stimuli exist. These sensors can be used in wearable flexible electronic devices, including resistive sensors responding to pressure, capacitive sensors responding to strain, piezoelectric sensors, and others. Their high-stress threshold, good self-healing properties, and relative resistance to damage make them highly suitable for such applications [162–169]. For example, Alshareef et al. proposed an MXene-based hydrogel by incorporating a type of 2D early-transition metal carbides/carbonitrides  $Ti_3C_2T_x$  nanosheets (MXenes) with high conductivity and hydrophilic surface into polyvinyl alcohol hydrogel. This hydrogel has excellent tensile strain sensitivity, significant stretchability of more than 3400%, instantaneous self-healing ability, and excellent conformability. Therefore, it shows excellent sensing performance in sensing applications and can be used as a wearable electronic device to sense the movement of various parts of the body [170]. As shown in Figure 7a, Cao et al. designed

single-layer composite hydrogels with bulk capacitive junctions as mechanical sensors. Dielectric peptide-coated graphene is engineered to serve as homogeneously dispersed electric double layers in hydrogels. Thus, the overall capacitance can be significantly changed by any mechanical motions that alter the microscopic distributions of peptide-coated graphene in the hydrogels. Peptide self-assembly is used to render strong yet dynamic interfacial interactions between the hydrogel network and graphene, allowing the hydrogels to be stretched up to 77 times their original length and self-heal in a few minutes [171].



**Figure 7.** Applications of different high-toughness hydrogels in flexible electronics. (a) Single-layer composite hydrogels with bulk capacitive junctions, which can serve as mechanical sensors. Reprinted with permission from Ref. [171]. 2022, Oxford University Press. (b) Schematic, properties, and applications of a super strong, stiff, and conductive alginate hydrogel with densely interconnecting networks. Reprinted with permission from Ref. [172]. 2022, Springer Nature. (c) Schematic, properties, and applications of a hydrogel crosslinked by double linkers of Laponite (synthetic hectorite-type clay) and graphene oxide, which can serve as supercapacitors. Reprinted with permission from Ref. [173]. 2019, Springer Nature.

Hydrogels with integrated conductive structures also hold great potential as conductive materials for use in brain-computer interfaces due to their good biocompatibility [174–177]. For example, Zhao et al. proposed a bi-continuous conducting polymer hydrogel, which simultaneously exhibits high electrical conductivity, stretchability, and fracture toughness. This hydrogel can also be 3D printed and used as a bioelectronic interface material to record and stimulate the long-term electrophysiological in rat models [178]. Another example is the protein-based bioprotonic hydrogel designed by Mao et al., which boasts reliable water retention capacity, antifreeze ability, stretchability, transparency, and biodegradability. This hydrogel can serve as an artificial bioprotonic skin for the long-term collection of high-quality human electrophysiological signals and self-powered sensing, which may even promote the development of novel human–machine merging interfaces [167]. In addition, Kim et al. demonstrated super strong, stiff, and conductive alginate hydrogels with densely interconnecting networks. They achieved this by anisotropic densification of Ca-Alg pre-gel and a subsequent ionic crosslinking with rehydration, as shown in Figure 7b. These hydrogels demonstrate exceptional tensile strengths (8–57 MPa) and elastic moduli (94–1290 MPa). Additionally, they exhibit strong interfacial adhesion, making them suitable as stable gel electrolyte membranes for use in aqueous supercapacitors [172].

Hydrogel flexible electronics also show promising applications in flexible energy storage devices [179–184]. For example, Guo et al. integrated a carbon nanotube con-

ductive network and an electrolyte salt into a flexible double-network hydrogel to create a hydrogel supercapacitor. This supercapacitor can deliver high areal capacitance and maintain stable energy output under various deformations [185]. In addition, Xie et al. constructed a surface-microstructured tough hydrogel electrolyte composed of agar/polyacrylamide/LiCl (AG/PAAm/LiCl). By attaching activated carbon electrodes, they successfully prepared stretchable supercapacitors capable of maintaining good electrochemical behavior and capacitance under large mechanical strains [186]. In addition, Chen et al. proposed a hydrogel of a copolymer crosslinked by double linkers of Laponite (synthetic hectorite-type clay) and graphene oxide, as shown in Figure 7c. This hydrogel exhibits high mechanical stretchability, excellent ionic conductivity, and superior healable performance [173]. The supercapacitors fabricated using this hydrogel as a gel electrolyte demonstrate repeated healable performance under treatments of both infrared light irradiation and heating, as well as stable electrical properties under stretching. It is worth noting that this supercapacitor has a stretchability of 900% with slightly reduced performance, even if it has defects.

#### 4. Outlook

High strength, toughness, and rapid recovery are inherent properties of many natural materials, such as biological tissues [187–190]. These properties have inspired the exploration of synthetic materials, particularly hydrogels, which have a wide range of potential applications, from biomedical devices to flexible electronic devices [191–196]. However, there are still many challenges in incorporating these properties into hydrogels due to the unique network structure and unique mechanical response of hydrogels. For example, in terms of preparation methods, more in situ gelation methods need to be developed to meet the need for rapid solidification of hydrogels in 3D printing. In terms of application scenarios, integrating anti-dehydration mechanisms such as grafted surface coatings would allow hydrogels to be stably stored long-term in various conditions and expand their application scope. Experimental, theoretical, and computational methods are indispensable tools in this pursuit. Simulation and modeling can provide insights into and predict the microstructural evolution and mechanical behavior of materials [197,198]. Finite element analysis and molecular dynamics simulations are particularly useful for understanding the interactions between various network characteristics and mechanical properties [171,199–203]. With the development of artificial intelligence (AI), machine learning can be used to train models on large experimental and simulated datasets to predict the composition and manufacturing conditions of optimal hydrogels [204–206]. After optimizing and improving the mechanical performance of hydrogels using AI, the manufacture of novel hydrogels can be achieved through proposed structural designs, significantly speeding up the development process.

The potential applications of these advanced tough hydrogels are vast and diverse. In the field of medicine, they can revolutionize skin repair techniques, serve as efficient artificial muscles for prosthetic limbs, enable precise drug delivery systems for targeted therapies, and provide scaffolding for tissue engineering, promoting the regeneration of damaged tissues. In the realm of soft robotics, their tunable mechanical properties make them versatile components that make them capable of functioning as actuators to drive movements, as sensors to detect environmental changes, or even as materials for human-bio interface applications, enhancing the interaction between humans and machines. Furthermore, their inherent self-healing abilities hold promise for creating durable and reusable materials across various industries, contributing to sustainable and cost-effective solutions. In addition, the fusion of tough hydrogel materials with synthetic biology has emerged as a leading force in the realms of biodegradable and reproducible functional materials, which are also so-called living hydrogels [207–211]. For example, Zhao et al. present a design for stretchable, robust, and biocompatible hydrogel–elastomer hybrids hosting various genetically engineered bacterial cells, combining the stretchability and robustness of tough hydrogels and biological functions of living bacterial cells [210].

In summary, by drawing inspiration from nature and leveraging experimentation, simulation, and artificial intelligence, hydrogels with high strength, toughness, and rapid recovery can be rationally designed and achieved. Future trends in hydrogel preparation will focus on creating tough, multifunctional, intelligent, and living materials, opening up new avenues in science and technology.

**Author Contributions:** Writing—original draft preparation, Z.X. and Y.C. (Yanru Chen); writing—review and editing, Z.X., Y.C. (Yi Cao) and B.X. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was mainly funded by the National Natural Science Foundation of China (grants Nos. T2322010 and T2225016), National Key R&D Program of China (Grant No. 2020YFA0908100), Natural Science Foundation of Jiangsu Province (grant No. BK20220120), Fundamental Research Funds for the Central Universities (grant No. 020514380274), and Shandong Provincial Laboratory Project (Grant No. SYS202202).

**Data Availability Statement:** All data are available in the main text.

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

## References

1. Kim, U.-J.; Park, J.; Li, C.; Jin, H.-J.; Valluzzi, R.; Kaplan, D.L. Structure and Properties of Silk Hydrogels. *Biomacromolecules* **2004**, *5*, 786–792. [[CrossRef](#)]
2. Griffith, L.G.; Naughton, G. Tissue Engineering—Current Challenges and Expanding Opportunities. *Science* **2002**, *295*, 1009–1014. [[CrossRef](#)]
3. Tang, J.D.; Mura, C.; Lampe, K.J. Stimuli-Responsive, Pentapeptide, Nanofiber Hydrogel for Tissue Engineering. *J. Am. Chem. Soc.* **2019**, *141*, 4886–4899. [[CrossRef](#)]
4. Gupta, A.; Kowalczyk, M.; Heaselgrave, W.; Britland, S.T.; Martin, C.; Radecka, I. The production and application of hydrogels for wound management: A review. *Eur. Polym. J.* **2019**, *111*, 134–151. [[CrossRef](#)]
5. Han, L.; Lu, X.; Liu, K.; Wang, K.; Fang, L.; Weng, L.-T.; Zhang, H.; Tang, Y.; Ren, F.; Zhao, C.; et al. Mussel-Inspired Adhesive and Tough Hydrogel Based on Nanoclay Confined Dopamine Polymerization. *ACS Nano* **2017**, *11*, 2561–2574. [[CrossRef](#)] [[PubMed](#)]
6. Gao, Y.; Wu, K.; Suo, Z. Photodetachable Adhesion. *Adv. Mater.* **2019**, *31*, 1806948. [[CrossRef](#)] [[PubMed](#)]
7. Wu, J.; Chen, A.; Qin, M.; Huang, R.; Zhang, G.; Xue, B.; Wei, J.; Li, Y.; Cao, Y.; Wang, W. Hierarchical construction of a mechanically stable peptide–graphene oxide hybrid hydrogel for drug delivery and pulsatile triggered release in vivo. *Nanoscale* **2015**, *7*, 1655–1660. [[CrossRef](#)] [[PubMed](#)]
8. Qu, J.; Liang, Y.; Shi, M.; Guo, B.; Gao, Y.; Yin, Z. Biocompatible conductive hydrogels based on dextran and aniline trimer as electro-responsive drug delivery system for localized drug release. *Int. J. Biol. Macromol.* **2019**, *140*, 255–264. [[CrossRef](#)]
9. Bassil, M.; Davenas, J.; El Tahchi, M. Electrochemical properties and actuation mechanisms of polyacrylamide hydrogel for artificial muscle application. *Sens. Actuators B Chem.* **2008**, *134*, 496–501. [[CrossRef](#)]
10. Cai, G.; Wang, J.; Qian, K.; Chen, J.; Li, S.; Lee, P.S. Extremely Stretchable Strain Sensors Based on Conductive Self-Healing Dynamic Cross-Links Hydrogels for Human-Motion Detection. *Adv. Sci.* **2017**, *4*, 1600190. [[CrossRef](#)]
11. Pan, S.; Zhang, F.; Cai, P.; Wang, M.; He, K.; Luo, Y.; Li, Z.; Chen, G.; Ji, S.; Liu, Z.; et al. Mechanically Interlocked Hydrogel–Elastomer Hybrids for On-Skin Electronics. *Adv. Funct. Mater.* **2020**, *30*, 1909540. [[CrossRef](#)]
12. Zhou, Y.; Wan, C.; Yang, Y.; Yang, H.; Wang, S.; Dai, Z.; Ji, K.; Jiang, H.; Chen, X.; Long, Y. Highly Stretchable, Elastic, and Ionic Conductive Hydrogel for Artificial Soft Electronics. *Adv. Funct. Mater.* **2019**, *29*, 1806220. [[CrossRef](#)]
13. Banerjee, H.; Suhail, M.; Ren, H. Hydrogel Actuators and Sensors for Biomedical Soft Robots: Brief Overview with Impending Challenges. *Biomimetics* **2018**, *3*, 15. [[CrossRef](#)]
14. Banerjee, H.; Ren, H. Optimizing Double-Network Hydrogel for Biomedical Soft Robots. *Soft Robot.* **2017**, *4*, 191–201. [[CrossRef](#)] [[PubMed](#)]
15. Ware, T.; Simon, D.; Rennaker, R.L.; Voit, W. Smart Polymers for Neural Interfaces. *Polym. Rev.* **2013**, *53*, 108–129. [[CrossRef](#)]
16. Guo, J.; Liu, M.; Zehnder, A.T.; Zhao, J.; Narita, T.; Creton, C.; Hui, C.-Y. Fracture mechanics of a self-healing hydrogel with covalent and physical crosslinks: A numerical study. *J. Mech. Phys. Solids* **2018**, *120*, 79–95. [[CrossRef](#)]
17. Lucantonio, A.; Noselli, G.; Trepast, X.; DeSimone, A.; Arroyo, M. Hydraulic Fracture and Toughening of a Brittle Layer Bonded to a Hydrogel. *Phys. Rev. Lett.* **2015**, *115*, 188105. [[CrossRef](#)]
18. Li, X.; Gong, J.P. Role of dynamic bonds on fatigue threshold of tough hydrogels. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2200678119. [[CrossRef](#)] [[PubMed](#)]
19. Ritchie, R.O. The conflicts between strength and toughness. *Nat. Mater.* **2011**, *10*, 817–822. [[CrossRef](#)]
20. Peak, C.W.; Wilker, J.J.; Schmidt, G. A review on tough and sticky hydrogels. *Colloid Polym. Sci.* **2013**, *291*, 2031–2047. [[CrossRef](#)]
21. Sun, J.-Y.; Zhao, X.; Illeperuma, W.R.K.; Chaudhuri, O.; Oh, K.H.; Mooney, D.J.; Vlassak, J.J.; Suo, Z. Highly stretchable and tough hydrogels. *Nature* **2012**, *489*, 133–136. [[CrossRef](#)] [[PubMed](#)]

22. Shi, F.-K.; Zhong, M.; Zhang, L.-Q.; Liu, X.-Y.; Xie, X.-M. Robust and self-healable nanocomposite physical hydrogel facilitated by the synergy of ternary crosslinking points in a single network. *J. Mater. Chem. B* **2016**, *4*, 6221–6227. [[CrossRef](#)]
23. Li, C.; Zhou, X.; Shao, Y.; Chen, P.; Xing, Y.; Yang, Z.; Li, Z.; Liu, D. A supramolecular hydrogel with identical cross-linking point density but distinctive rheological properties. *Mater. Chem. Front.* **2017**, *1*, 654–659. [[CrossRef](#)]
24. Sakai, T.; Matsunaga, T.; Yamamoto, Y.; Ito, C.; Yoshida, R.; Suzuki, S.; Sasaki, N.; Shibayama, M.; Chung, U.-I. Design and Fabrication of a High-Strength Hydrogel with Ideally Homogeneous Network Structure from Tetrahedron-like Macromonomers. *Macromolecules* **2008**, *41*, 5379–5384. [[CrossRef](#)]
25. Pan, W.; Wen, H.; Niu, L.; Su, C.; Liu, C.; Zhao, J.; Mao, C.; Liang, D. Effects of chain flexibility on the properties of DNA hydrogels. *Soft Matter* **2016**, *12*, 5537–5541. [[CrossRef](#)]
26. Ahmed, E.M. Hydrogel: Preparation, characterization, and applications: A review. *J. Adv. Res.* **2015**, *6*, 105–121. [[CrossRef](#)] [[PubMed](#)]
27. Chen, Q.; Chen, H.; Zhu, L.; Zheng, J. Fundamentals of double network hydrogels. *J. Mater. Chem. B* **2015**, *3*, 3654–3676. [[CrossRef](#)] [[PubMed](#)]
28. Chen, H.; Chen, Q.; Hu, R.; Wang, H.; Newby, B.-M.Z.; Chang, Y.; Zheng, J. Mechanically strong hybrid double network hydrogels with antifouling properties. *J. Mater. Chem. B* **2015**, *3*, 5426–5435. [[CrossRef](#)]
29. Nakayama, A.; Kakugo, A.; Gong, J.P.; Osada, Y.; Takai, M.; Erata, T.; Kawano, S. High Mechanical Strength Double-Network Hydrogel with Bacterial Cellulose. *Adv. Funct. Mater.* **2004**, *14*, 1124–1128. [[CrossRef](#)]
30. Creton, C. 50th Anniversary Perspective: Networks and Gels: Soft but Dynamic and Tough. *Macromolecules* **2017**, *50*, 8297–8316. [[CrossRef](#)]
31. Shao, C.; Chang, H.; Wang, M.; Xu, F.; Yang, J. High-Strength, Tough, and Self-Healing Nanocomposite Physical Hydrogels Based on the Synergistic Effects of Dynamic Hydrogen Bond and Dual Coordination Bonds. *ACS Appl. Mater. Interfaces* **2017**, *9*, 28305–28318. [[CrossRef](#)]
32. Lei, Y.; Zhang, G.; Jiang, H.; Li, F.; Liu, H.; Xia, Y.; Zhang, Y.; Xin, F.; Zhang, X.; Li, H. Synergistic toughening of nanocomposite hydrogel based on ultrasmall aluminum hydroxide nanoparticles and hydroxyapatite nanoparticles. *Polym. Compos.* **2019**, *40*, 942–951. [[CrossRef](#)]
33. Ishii, S.; Kokubo, H.; Hashimoto, K.; Imaizumi, S.; Watanabe, M. Tetra-PEG Network Containing Ionic Liquid Synthesized via Michael Addition Reaction and Its Application to Polymer Actuator. *Macromolecules* **2017**, *50*, 2906–2915. [[CrossRef](#)]
34. Zheng, S.Y.; Liu, C.; Jiang, L.; Lin, J.; Qian, J.; Mayumi, K.; Wu, Z.L.; Ito, K.; Zheng, Q. Slide-Ring Cross-Links Mediated Tough Metallosupramolecular Hydrogels with Superior Self-Recoverability. *Macromolecules* **2019**, *52*, 6748–6755. [[CrossRef](#)]
35. Bin Imran, A.; Esaki, K.; Gotoh, H.; Seki, T.; Ito, K.; Sakai, Y.; Takeoka, Y. Extremely stretchable thermosensitive hydrogels by introducing slide-ring polyrotaxane cross-linkers and ionic groups into the polymer network. *Nat. Commun.* **2014**, *5*, 5124. [[CrossRef](#)] [[PubMed](#)]
36. Chung, H.-J.; Charaya, H.; Liu, L.; Li, X. Tough Hydrogels: Toughening Mechanisms and Their Utilization in Stretchable Electronics and in Regenerative Medicines. In *Hybrid Organic-Inorganic Interfaces*; John Wiley and Sons: Hoboken, NJ, USA, 2018; pp. 535–580.
37. Kuang, X.; Arican, M.O.; Zhou, T.; Zhao, X.; Zhang, Y.S. Functional Tough Hydrogels: Design, Processing, and Biomedical Applications. *Acc. Mater. Res.* **2023**, *4*, 101–114. [[CrossRef](#)]
38. Zhao, X. Multi-scale multi-mechanism design of tough hydrogels: Building dissipation into stretchy networks. *Soft Matter* **2014**, *10*, 672–687. [[CrossRef](#)] [[PubMed](#)]
39. Wu, X.; Huang, W.; Wu, W.-H.; Xue, B.; Xiang, D.; Li, Y.; Qin, M.; Sun, F.; Wang, W.; Zhang, W.-B.; et al. Reversible hydrogels with tunable mechanical properties for optically controlling cell migration. *Nano Res.* **2018**, *11*, 5556–5565. [[CrossRef](#)]
40. Xiang, D.; Wu, X.; Cao, W.; Xue, B.; Qin, M.; Cao, Y.; Wang, W. Hydrogels With Tunable Mechanical Properties Based on Photocleavable Proteins. *Front. Chem.* **2020**, *8*, 7. [[CrossRef](#)]
41. Lin, P.; Zhang, T.; Wang, X.; Yu, B.; Zhou, F. Freezing Molecular Orientation under Stretch for High Mechanical Strength but Anisotropic Hydrogels. *Small* **2016**, *12*, 4386–4392. [[CrossRef](#)]
42. Wu, Q.; Wei, J.; Xu, B.; Liu, X.; Wang, H.; Wang, W.; Wang, Q.; Liu, W. A robust, highly stretchable supramolecular polymer conductive hydrogel with self-healability and thermo-processability. *Sci. Rep.* **2017**, *7*, 41566. [[CrossRef](#)]
43. Lian, W.Z.; Fan, Z.W.; Cui, K.; Yin, P.; Yang, J.; Jiang, H.; Tang, L.; Sun, T. Tough Hydrogels with Dynamic H-Bonds: Structural Heterogeneities and Mechanical Performances. *Macromolecules* **2021**, *54*, 8996–9006. [[CrossRef](#)]
44. Wang, Y.J.; Zhang, X.N.; Song, Y.; Zhao, Y.; Chen, L.; Su, F.; Li, L.; Wu, Z.L.; Zheng, Q. Ultrastiff and Tough Supramolecular Hydrogels with a Dense and Robust Hydrogen Bond Network. *Chem. Mater.* **2019**, *31*, 1430–1440. [[CrossRef](#)]
45. Sun, W.; Xue, B.; Fan, Q.; Tao, R.; Wang, C.; Wang, X.; Li, Y.; Qin, M.; Wang, W.; Chen, B.; et al. Molecular engineering of metal coordination interactions for strong, tough, and fast-recovery hydrogels. *Sci. Adv.* **2020**, *6*, eaz9531. [[CrossRef](#)]
46. Sun, T.L.; Kurokawa, T.; Kuroda, S.; Ihsan, A.B.; Akasaki, T.; Sato, K.; Haque, M.A.; Nakajima, T.; Gong, J.P. Physical hydrogels composed of polyampholytes demonstrate high toughness and viscoelasticity. *Nat. Mater.* **2013**, *12*, 932–937. [[CrossRef](#)]
47. Hu, X.; Vatankhah-Varnoosfaderani, M.; Zhou, J.; Li, Q.; Sheiko, S.S. Weak Hydrogen Bonding Enables Hard, Strong, Tough, and Elastic Hydrogels. *Adv. Mater.* **2015**, *27*, 6899–6905. [[CrossRef](#)]
48. Dai, X.; Zhang, Y.; Gao, L.; Bai, T.; Wang, W.; Cui, Y.; Liu, W. A Mechanically Strong, Highly Stable, Thermoplastic, and Self-Healable Supramolecular Polymer Hydrogel. *Adv. Mater.* **2015**, *27*, 3566–3571. [[CrossRef](#)] [[PubMed](#)]

49. Long, T.; Li, Y.; Fang, X.; Sun, J. Salt-Mediated Polyampholyte Hydrogels with High Mechanical Strength, Excellent Self-Healing Property, and Satisfactory Electrical Conductivity. *Adv. Funct. Mater.* **2018**, *28*, 1804416. [[CrossRef](#)]
50. Xue, B.; Qin, M.; Wang, T.; Wu, J.; Luo, D.; Jiang, Q.; Li, Y.; Cao, Y.; Wang, W. Electrically Controllable Actuators Based on Supramolecular Peptide Hydrogels. *Adv. Funct. Mater.* **2016**, *26*, 9053–9062. [[CrossRef](#)]
51. Xia, Y.; Xue, B.; Qin, M.; Cao, Y.; Li, Y.; Wang, W. Printable Fluorescent Hydrogels Based on Self-Assembling Peptides. *Sci. Rep.* **2017**, *7*, 9691. [[CrossRef](#)]
52. Wei, Z.; Yang, J.H.; Liu, Z.Q.; Xu, F.; Zhou, J.X.; Zrínyi, M.; Osada, Y.; Chen, Y.M. Novel Biocompatible Polysaccharide-Based Self-Healing Hydrogel. *Adv. Funct. Mater.* **2015**, *25*, 1352–1359. [[CrossRef](#)]
53. Li, L.; Yan, B.; Yang, J.; Chen, L.; Zeng, H. Novel Mussel-Inspired Injectable Self-Healing Hydrogel with Anti-Biofouling Property. *Adv. Mater.* **2015**, *27*, 1294–1299. [[CrossRef](#)]
54. Liu, J.; Tan, C.S.Y.; Yu, Z.; Li, N.; Abell, C.; Scherman, O.A. Tough Supramolecular Polymer Networks with Extreme Stretchability and Fast Room-Temperature Self-Healing. *Adv. Mater.* **2017**, *29*, 1605325. [[CrossRef](#)] [[PubMed](#)]
55. Li, Y.; Yan, J.; Liu, Y.; Xie, X.-M. Super Tough and Intelligent Multibond Network Physical Hydrogels Facilitated by Ti3C2Tx MXene Nanosheets. *ACS Nano* **2022**, *16*, 1567–1577. [[CrossRef](#)] [[PubMed](#)]
56. Chakraborty, A.; Pacelli, S.; Alexander, S.; Huayamares, S.; Rosenkrans, Z.; Vergel, F.E.; Wu, Y.; Chakravorty, A.; Paul, A. Nanoparticle-Reinforced Tough Hydrogel as a Versatile Platform for Pharmaceutical Drug Delivery: Preparation and in Vitro Characterization. *Mol. Pharm.* **2023**, *20*, 767–774. [[CrossRef](#)] [[PubMed](#)]
57. Zhang, Y.S.; Khademhosseini, A. Advances in engineering hydrogels. *Science* **2017**, *356*, eaaf3627. [[CrossRef](#)] [[PubMed](#)]
58. Su, T.; Zhang, D.; Tang, Z.; Wu, Q.; Wang, Q. HRP-mediated polymerization forms tough nanocomposite hydrogels with high biocatalytic performance. *Chem. Commun.* **2013**, *49*, 8033–8035. [[CrossRef](#)] [[PubMed](#)]
59. Gaharwar, A.K.; Peppas, N.A.; Khademhosseini, A. Nanocomposite hydrogels for biomedical applications. *Biotechnol. Bioeng.* **2014**, *111*, 441–453. [[CrossRef](#)]
60. Li, Z.; Hou, Z.; Fan, H.; Li, H. Organic–Inorganic Hierarchical Self-Assembly into Robust Luminescent Supramolecular Hydrogel. *Adv. Funct. Mater.* **2017**, *27*, 1604379. [[CrossRef](#)]
61. Sun, G.; Li, Z.; Liang, R.; Weng, L.-T.; Zhang, L. Super stretchable hydrogel achieved by non-aggregated spherulites with diameters <5 nm. *Nat. Commun.* **2016**, *7*, 12095. [[CrossRef](#)]
62. Xiong, J.; Wang, X.; Li, L.; Li, Q.; Zheng, S.; Liu, Z.; Li, W.; Yan, F. Low-Hysteresis and High-Toughness Hydrogels Regulated by Porous Cationic Polymers: The Effect of Counteranions. *Angew. Chem. Int. Ed.* **2024**, *63*, e202316375. [[CrossRef](#)] [[PubMed](#)]
63. Schütt, F.; Signetti, S.; Krüger, H.; Röder, S.; Smazna, D.; Kaps, S.; Gorb, S.N.; Mishra, Y.K.; Pugno, N.M.; Adelung, R. Hierarchical self-entangled carbon nanotube tube networks. *Nat. Commun.* **2017**, *8*, 1215. [[CrossRef](#)] [[PubMed](#)]
64. Ma, P.-C.; Siddiqui, N.A.; Marom, G.; Kim, J.-K. Dispersion and functionalization of carbon nanotubes for polymer-based nanocomposites: A review. *Compos. Part A Appl. Sci. Manuf.* **2010**, *41*, 1345–1367. [[CrossRef](#)]
65. Rehman, H.U.; Chen, Y.; Guo, Y.; Du, Q.; Zhou, J.; Guo, Y.; Duan, H.; Li, H.; Liu, H. Stretchable, strong and self-healing hydrogel by oxidized CNT-polymer composite. *Compos. Part A Appl. Sci. Manuf.* **2016**, *90*, 250–260. [[CrossRef](#)]
66. Zhao, X.; Guo, B.; Wu, H.; Liang, Y.; Ma, P.X. Injectable antibacterial conductive nanocomposite cryogels with rapid shape recovery for noncompressible hemorrhage and wound healing. *Nat. Commun.* **2018**, *9*, 2784. [[CrossRef](#)]
67. Haraguchi, K.; Takehisa, T. Nanocomposite Hydrogels: A Unique Organic–Inorganic Network Structure with Extraordinary Mechanical, Optical, and Swelling/De-swelling Properties. *Adv. Mater.* **2002**, *14*, 1120–1124. [[CrossRef](#)]
68. Han, L.; Lu, X.; Wang, M.; Gan, D.; Deng, W.; Wang, K.; Fang, L.; Liu, K.; Chan, C.W.; Tang, Y.; et al. A Mussel-Inspired Conductive, Self-Adhesive, and Self-Healable Tough Hydrogel as Cell Stimulators and Implantable Bioelectronics. *Small* **2017**, *13*, 1601916. [[CrossRef](#)]
69. Luo, C.; Wang, W.; Yang, W.; Liu, X.; Lin, J.; Zhang, L.; He, S. High-Strength and Multi-Recyclable Epoxy Vitrimer Containing Dual-Dynamic Covalent Bonds Based on the Disulfide and Imine Bond Metathesis. *ACS Sustain. Chem. Eng.* **2023**, *11*, 14591–14600. [[CrossRef](#)]
70. Hammer, L.; Van Zee, N.J.; Nicolaÿ, R. Dually Crosslinked Polymer Networks Incorporating Dynamic Covalent Bonds. *Polymers* **2021**, *13*, 396. [[CrossRef](#)]
71. Bui, K.; Nguyen, G.T.; Vancaeyzeele, C.; Vidal, F.; Hu, X.; Wan, C.; Plesse, C. Stretchable, healable, and weldable vitrimer ionogel for ionotronic applications. *Chem. Eng. J.* **2023**, *474*, 145533. [[CrossRef](#)]
72. Gong, J.P. Materials both Tough and Soft. *Science* **2014**, *344*, 161–162. [[CrossRef](#)]
73. Gong, J.P. Why are double network hydrogels so tough? *Soft Matter* **2010**, *6*, 2583–2590. [[CrossRef](#)]
74. Chen, Q.; Zhu, L.; Chen, H.; Yan, H.; Huang, L.; Yang, J.; Zheng, J. A Novel Design Strategy for Fully Physically Linked Double Network Hydrogels with Tough, Fatigue Resistant, and Self-Healing Properties. *Adv. Funct. Mater.* **2015**, *25*, 1598–1607. [[CrossRef](#)]
75. Gong, J.P.; Katsuyama, Y.; Kurokawa, T.; Osada, Y. Double-Network Hydrogels with Extremely High Mechanical Strength. *Adv. Mater.* **2003**, *15*, 1155–1158. [[CrossRef](#)]
76. Gan, D.; Xing, W.; Jiang, L.; Fang, J.; Zhao, C.; Ren, F.; Fang, L.; Wang, K.; Lu, X. Plant-inspired adhesive and tough hydrogel based on Ag-Lignin nanoparticles-triggered dynamic redox catechol chemistry. *Nat. Commun.* **2019**, *10*, 1487. [[CrossRef](#)]
77. Sun, W.; Xue, B.; Li, Y.; Qin, M.; Wu, J.; Lu, K.; Wu, J.; Cao, Y.; Jiang, Q.; Wang, W. Polymer-Supramolecular Polymer Double-Network Hydrogel. *Adv. Funct. Mater.* **2016**, *26*, 9044–9052. [[CrossRef](#)]

78. Nakajima, T.; Furukawa, H.; Tanaka, Y.; Kurokawa, T.; Osada, Y.; Gong, J.P. True chemical structure of double network hydrogels. *Macromolecules* **2009**, *42*, 2184–2189. [[CrossRef](#)]
79. Yang, Y.; Wang, X.; Yang, F.; Wang, L.; Wu, D. Highly Elastic and Ultratough Hybrid Ionic–Covalent Hydrogels with Tunable Structures and Mechanics. *Adv. Mater.* **2018**, *30*, 1707071. [[CrossRef](#)] [[PubMed](#)]
80. Gonzalez, M.A.; Simon, J.R.; Ghoorchian, A.; Scholl, Z.; Lin, S.; Rubinstein, M.; Marszalek, P.; Chilkoti, A.; López, G.P.; Zhao, X. Strong, Tough, Stretchable, and Self-Adhesive Hydrogels from Intrinsically Unstructured Proteins. *Adv. Mater.* **2017**, *29*, 1604743. [[CrossRef](#)]
81. Hu, X.; Zhou, J.; Daniel, W.F.M.; Vatankeh-Varnoosfaderani, M.; Dobrynin, A.V.; Sheiko, S.S. Dynamics of Dual Networks: Strain Rate and Temperature Effects in Hydrogels with Reversible H-Bonds. *Macromolecules* **2017**, *50*, 652–659. [[CrossRef](#)]
82. Lin, P.; Ma, S.; Wang, X.; Zhou, F. Molecularly Engineered Dual-Crosslinked Hydrogel with Ultrahigh Mechanical Strength, Toughness, and Good Self-Recovery. *Adv. Mater.* **2015**, *27*, 2054–2059. [[CrossRef](#)]
83. Grindy, S.C.; Learsch, R.; Mozhdzhi, D.; Cheng, J.; Barrett, D.G.; Guan, Z.; Messersmith, P.B.; Holten-Andersen, N. Control of hierarchical polymer mechanics with bioinspired metal-coordination dynamics. *Nat. Mater.* **2015**, *14*, 1210–1216. [[CrossRef](#)]
84. Fullenkamp, D.E.; He, L.; Barrett, D.G.; Burghardt, W.R.; Messersmith, P.B. Mussel-Inspired Histidine-Based Transient Network Metal Coordination Hydrogels. *Macromolecules* **2013**, *46*, 1167–1174. [[CrossRef](#)]
85. Bai, R.; Yang, Q.; Tang, J.; Morelle, X.P.; Vlassak, J.; Suo, Z. Fatigue fracture of tough hydrogels. *Extrem. Mech. Lett.* **2017**, *15*, 91–96. [[CrossRef](#)]
86. Mow, V.C.; Lai, W.M. Recent Developments in Synovial Joint Biomechanics. *SIAM Rev.* **1980**, *22*, 275–317. [[CrossRef](#)]
87. Wang, T.; Zhang, Y.; Gu, Z.; Cheng, W.; Lei, H.; Qin, M.; Xue, B.; Wang, W.; Cao, Y. Regulating Mechanical Properties of Polymer-Supramolecular Double-Network Hydrogel by Supramolecular Self-assembling Structures. *Chin. J. Chem.* **2021**, *39*, 2711–2717. [[CrossRef](#)]
88. Zhang, H.J.; Sun, T.L.; Zhang, A.K.; Ikura, Y.; Nakajima, T.; Nonoyama, T.; Kurokawa, T.; Ito, O.; Ishitobi, H.; Gong, J.P. Tough Physical Double-Network Hydrogels Based on Amphiphilic Triblock Copolymers. *Adv. Mater.* **2016**, *28*, 4884–4890. [[CrossRef](#)] [[PubMed](#)]
89. Wang, W.; Zhang, Y.; Liu, W. Bioinspired fabrication of high strength hydrogels from non-covalent interactions. *Prog. Polym. Sci.* **2017**, *71*, 1–25. [[CrossRef](#)]
90. Li, J.; Suo, Z.; Vlassak, J.J. Stiff, strong, and tough hydrogels with good chemical stability. *J. Mater. Chem. B* **2014**, *2*, 6708–6713. [[CrossRef](#)] [[PubMed](#)]
91. Chen, Q.; Zhu, L.; Zhao, C.; Wang, Q.; Zheng, J. A Robust, One-Pot Synthesis of Highly Mechanical and Recoverable Double Network Hydrogels Using Thermoreversible Sol-Gel Polysaccharide. *Adv. Mater.* **2013**, *25*, 4171–4176. [[CrossRef](#)]
92. Zhang, L.; Fu, L.; Zhang, X.; Chen, L.; Cai, Q.; Yang, X. Hierarchical and heterogeneous hydrogel system as a promising strategy for diversified interfacial tissue regeneration. *Biomater. Sci.* **2021**, *9*, 1547–1573. [[CrossRef](#)]
93. An, Y.; Gao, L.; Wang, T. Graphene Oxide/Alginate Hydrogel Fibers with Hierarchically Arranged Helical Structures for Soft Actuator Application. *ACS Appl. Nano Mater.* **2020**, *3*, 5079–5087. [[CrossRef](#)]
94. Wang, Z.; Xu, X.; Tan, R.; Zhang, S.; Zhang, K.; Hu, J. Hierarchically Structured Hydrogel Composites with Ultra-High Conductivity for Soft Electronics. *Adv. Funct. Mater.* **2023**, 2312667. [[CrossRef](#)]
95. Guo, Q.; Liu, Y.; Liu, J.; Wang, Y.; Cui, Q.; Song, P.; Zhang, X.; Zhang, C. Hierarchically Structured Hydrogel Actuator for Microplastic Pollutant Detection and Removal. *Chem. Mater.* **2022**, *34*, 5165–5175. [[CrossRef](#)]
96. Liu, K.; Zang, S.; Xue, R.; Yang, J.; Wang, L.; Huang, J.; Yan, Y. Coordination-Triggered Hierarchical Folate/Zinc Supramolecular Hydrogels Leading to Printable Biomaterials. *ACS Appl. Mater. Interfaces* **2018**, *10*, 4530–4539. [[CrossRef](#)]
97. Garg, V.; Gupta, T.; Rani, S.; Bandyopadhyay-Ghosh, S.; Ghosh, S.B.; Qiao, L.; Liu, G. A hierarchically designed nanocomposite hydrogel with multisensory capabilities towards wearable devices for human-body motion and glucose concentration detection. *Compos. Sci. Technol.* **2021**, *213*, 108894. [[CrossRef](#)]
98. Mredha, M.T.I.; Guo, Y.Z.; Nonoyama, T.; Nakajima, T.; Kurokawa, T.; Gong, J.P. A Facile Method to Fabricate Anisotropic Hydrogels with Perfectly Aligned Hierarchical Fibrous Structures. *Adv. Mater.* **2018**, *30*, 1704937. [[CrossRef](#)] [[PubMed](#)]
99. Hilderbrand, A.M.; Ford, E.M.; Guo, C.; Sloppy, J.D.; Kloxin, A.M. Hierarchically structured hydrogels utilizing multifunctional assembling peptides for 3D cell culture. *Biomater. Sci.* **2020**, *8*, 1256–1269. [[CrossRef](#)] [[PubMed](#)]
100. Sano, K.; Ishida, Y.; Aida, T. Synthesis of Anisotropic Hydrogels and Their Applications. *Angew. Chem. Int. Ed.* **2018**, *57*, 2532–2543. [[CrossRef](#)] [[PubMed](#)]
101. Liang, X.; Chen, G.; Lei, I.M.; Zhang, P.; Wang, Z.; Chen, X.; Lu, M.; Zhang, J.; Wang, Z.; Sun, T.; et al. Impact-Resistant Hydrogels by Harnessing 2D Hierarchical Structures. *Adv. Mater.* **2023**, *35*, 2207587. [[CrossRef](#)]
102. Hua, M.; Wu, S.; Ma, Y.; Zhao, Y.; Chen, Z.; Frenkel, I.; Strzalka, J.; Zhou, H.; Zhu, X.; He, X. Strong tough hydrogels via the synergy of freeze-casting and salting out. *Nature* **2021**, *590*, 594–599. [[CrossRef](#)] [[PubMed](#)]
103. Zhao, Y.; Zhang, B.; Yao, B.; Qiu, Y.; Peng, Z.; Zhang, Y.; Alsaied, Y.; Frenkel, I.; Youssef, K.; Pei, Q.; et al. Hierarchically Structured Stretchable Conductive Hydrogels for High-Performance Wearable Strain Sensors and Supercapacitors. *Matter* **2020**, *3*, 1196–1210. [[CrossRef](#)]
104. Guo, X.; Dong, X.; Zou, G.; Gao, H.; Zhai, W. Strong and tough fibrous hydrogels reinforced by multiscale hierarchical structures with multimechanisms. *Sci. Adv.* **2023**, *9*, eadf7075. [[CrossRef](#)] [[PubMed](#)]

105. Zhu, S.; Wang, S.; Huang, Y.; Tang, Q.; Fu, T.; Su, R.; Fan, C.; Xia, S.; Lee, P.S.; Lin, Y. Bioinspired structural hydrogels with highly ordered hierarchical orientations by flow-induced alignment of nanofibrils. *Nat. Commun.* **2024**, *15*, 118. [[CrossRef](#)]
106. Williams, A.H.; Roh, S.; Jacob, A.R.; Stoyanov, S.D.; Hsiao, L.; Veleev, O.D. Printable homocomposite hydrogels with synergistically reinforced molecular-colloidal networks. *Nat. Commun.* **2021**, *12*, 2834. [[CrossRef](#)] [[PubMed](#)]
107. Yu, H.-P.; Zhu, Y.-J. Bioinspired flexible, high-strength, and versatile hydrogel with the fiberboard-and-mortar hierarchically ordered structure. *Nano Res.* **2021**, *14*, 3643–3652. [[CrossRef](#)]
108. Mredha, M.T.I.; Le, H.H.; Tran, V.T.; Trtik, P.; Cui, J.; Jeon, I. Anisotropic tough multilayer hydrogels with programmable orientation. *Mater. Horiz.* **2019**, *6*, 1504–1511. [[CrossRef](#)]
109. Puza, F.; Zheng, Y.; Han, L.; Xue, L.; Cui, J. Physical entanglement hydrogels: Ultrahigh water content but good toughness and stretchability. *Polym. Chem.* **2020**, *11*, 2339–2345. [[CrossRef](#)]
110. Sugimura, A.; Asai, M.; Matsunaga, T.; Akagi, Y.; Sakai, T.; Noguchi, H.; Shibayama, M. Mechanical properties of a polymer network of Tetra-PEG gel. *Polym. J.* **2013**, *45*, 300–306. [[CrossRef](#)]
111. Matsunaga, T.; Sakai, T.; Akagi, Y.; Chung, U.-I.; Shibayama, M. Structure Characterization of Tetra-PEG Gel by Small-Angle Neutron Scattering. *Macromolecules* **2009**, *42*, 1344–1351. [[CrossRef](#)]
112. Sakai, T. Gelation mechanism and mechanical properties of Tetra-PEG gel. *React. Funct. Polym.* **2013**, *73*, 898–903. [[CrossRef](#)]
113. Xu, K.; Liang, X.; Li, P.; Deng, Y.; Pei, X.; Tan, Y.; Zhai, K.; Wang, P. Tough, stretchable chemically cross-linked hydrogel using core-shell polymer microspheres as cross-linking junctions. *Polymer* **2017**, *118*, 58–67. [[CrossRef](#)]
114. Fukasawa, M.; Sakai, T.; Chung, U.-I.; Haraguchi, K. Synthesis and Mechanical Properties of a Nanocomposite Gel Consisting of a Tetra-PEG/Clay Network. *Macromolecules* **2010**, *43*, 4370–4378. [[CrossRef](#)]
115. Tonsomboon, K.; Butcher, A.L.; Oyen, M.L. Strong and tough nanofibrous hydrogel composites based on biomimetic principles. *Mater. Sci. Eng. C* **2017**, *72*, 220–227. [[CrossRef](#)] [[PubMed](#)]
116. Kim, J.; Zhang, G.; Shi, M.; Suo, Z. Fracture, fatigue, and friction of polymers in which entanglements greatly outnumber cross-links. *Science* **2021**, *374*, 212–216. [[CrossRef](#)] [[PubMed](#)]
117. Tsukeshiba, H.; Huang, M.; Na, Y.-H.; Kurokawa, T.; Kuwabara, R.; Tanaka, Y.; Furukawa, H.; Osada, Y.; Gong, J.P. Effect of Polymer Entanglement on the Toughening of Double Network Hydrogels. *J. Phys. Chem. B* **2005**, *109*, 16304–16309. [[CrossRef](#)] [[PubMed](#)]
118. Zeng, Z.; Li, Z.; Li, Q.; Song, G.; Huo, M. Strong and Tough Nanostructured Hydrogels and Organogels Prepared by Polymerization-Induced Self-Assembly. *Small Methods* **2023**, *7*, 2201592. [[CrossRef](#)] [[PubMed](#)]
119. Fu, L.; Li, L.; Bian, Q.; Xue, B.; Jin, J.; Li, J.; Cao, Y.; Jiang, Q.; Li, H. Cartilage-like protein hydrogels engineered via entanglement. *Nature* **2023**, *618*, 740–747. [[CrossRef](#)]
120. Kubota, R.; Naritomi, M.; Fujimoto, I. Synthesis of a stretchable polymer crosslinker for reinforced atelocollagen threads. *React. Funct. Polym.* **2023**, *182*, 105462. [[CrossRef](#)]
121. Liu, C.; Morimoto, N.; Jiang, L.; Kawahara, S.; Noritomi, T.; Yokoyama, H.; Mayumi, K.; Ito, K. Tough hydrogels with rapid self-reinforcement. *Science* **2021**, *372*, 1078–1081. [[CrossRef](#)]
122. Lu, X.; Chan, C.Y.; Lee, K.I.; Ng, P.F.; Fei, B.; Xin, J.H.; Fu, J. Super-tough and thermo-healable hydrogel—Promising for shape-memory absorbent fiber. *J. Mater. Chem. B* **2014**, *2*, 7631–7638. [[CrossRef](#)]
123. Du, C.; Zhang, X.N.; Sun, T.L.; Du, M.; Zheng, Q.; Wu, Z.L. Hydrogen-Bond Association-Mediated Dynamics and Viscoelastic Properties of Tough Supramolecular Hydrogels. *Macromolecules* **2021**, *54*, 4313–4325. [[CrossRef](#)]
124. Chen, G.; Zhang, Q.; Ma, L.; Zhao, Y.; Ran, J. Rational Design of a High-Strength Tough Hydrogel from Fundamental Principles. *Macromol. Chem. Phys.* **2021**, *222*, 2100064. [[CrossRef](#)]
125. Wang, Z.; Zheng, X.; Ouchi, T.; Kouznetsova, T.B.; Beech, H.K.; Av-Ron, S.; Matsuda, T.; Bowser, B.H.; Wang, S.; Johnson, J.A.; et al. Toughening hydrogels through force-triggered chemical reactions that lengthen polymer strands. *Science* **2021**, *374*, 193–196. [[CrossRef](#)]
126. Xue, B.; Bashir, Z.; Guo, Y.; Yu, W.; Sun, W.; Li, Y.; Zhang, Y.; Qin, M.; Wang, W.; Cao, Y. Strong, tough, rapid-recovery, and fatigue-resistant hydrogels made of picot peptide fibres. *Nat. Commun.* **2023**, *14*, 2583. [[CrossRef](#)]
127. Hua, J.; Liu, C.; Ng, P.F.; Fei, B. Bacterial cellulose reinforced double-network hydrogels for shape memory strand. *Carbohydr. Polym.* **2021**, *259*, 117737. [[CrossRef](#)]
128. Wu, J.; Li, P.; Dong, C.; Jiang, H.; Bin, X.; Gao, X.; Qin, M.; Wang, W.; Bin, C.; Cao, Y. Rationally designed synthetic protein hydrogels with predictable mechanical properties. *Nat. Commun.* **2018**, *9*, 620. [[CrossRef](#)]
129. Zhu, F.; Cheng, L.; Wang, Z.J.; Hong, W.; Wu, Z.L.; Yin, J.; Qian, J.; Zheng, Q. 3D-Printed Ultratough Hydrogel Structures with Titin-like Domains. *ACS Appl. Mater. Interfaces* **2017**, *9*, 11363–11367. [[CrossRef](#)] [[PubMed](#)]
130. Shao, C.; Meng, L.; Wang, M.; Cui, C.; Wang, B.; Han, C.-R.; Xu, F.; Yang, J. Mimicking Dynamic Adhesiveness and Strain-Stiffening Behavior of Biological Tissues in Tough and Self-Healable Cellulose Nanocomposite Hydrogels. *ACS Appl. Mater. Interfaces* **2019**, *11*, 5885–5895. [[CrossRef](#)] [[PubMed](#)]
131. Sabzi, M.; Samadi, N.; Abbasi, F.; Mahdavinia, G.R.; Babaahmadi, M. Bioinspired fully physically cross-linked double network hydrogels with a robust, tough and self-healing structure. *Mater. Sci. Eng. C* **2017**, *74*, 374–381. [[CrossRef](#)] [[PubMed](#)]
132. Zhou, Y.; Liao, S.; Tao, X.; Xu, X.-Q.; Hong, Q.; Wu, D.; Wang, Y. Spider-Inspired Multicomponent 3D Printing Technique for Next-Generation Complex Biofabrication. *ACS Appl. Bio Mater.* **2018**, *1*, 502–510. [[CrossRef](#)] [[PubMed](#)]
133. Zhou, Y.; Gui, Q.; Yu, W.; Liao, S.; He, Y.; Tao, X.; Yu, Y.; Wang, Y. Interfacial Diffusion Printing: An Efficient Manufacturing Technique for Artificial Tubular Grafts. *ACS Biomater. Sci. Eng.* **2019**, *5*, 6311–6318. [[CrossRef](#)] [[PubMed](#)]

134. Zhai, X.; Ma, Y.; Hou, C.; Gao, F.; Zhang, Y.; Ruan, C.; Pan, H.; Lu, W.W.; Liu, W. 3D-Printed High Strength Bioactive Supramolecular Polymer/Clay Nanocomposite Hydrogel Scaffold for Bone Regeneration. *ACS Biomater. Sci. Eng.* **2017**, *3*, 1109–1118. [[CrossRef](#)] [[PubMed](#)]
135. Qiao, Z.; Parks, J.; Choi, P.; Ji, H.-F. Applications of Highly Stretchable and Tough Hydrogels. *Polymers* **2019**, *11*, 1773. [[CrossRef](#)] [[PubMed](#)]
136. Drury, J.L.; Mooney, D.J. Hydrogels for tissue engineering: Scaffold design variables and applications. *Biomaterials* **2003**, *24*, 4337–4351. [[CrossRef](#)]
137. Bodugoz-Senturk, H.; Macias, C.E.; Kung, J.H.; Muratoglu, O.K. Poly(vinyl alcohol)–acrylamide hydrogels as load-bearing cartilage substitute. *Biomaterials* **2009**, *30*, 589–596. [[CrossRef](#)]
138. Moutos, F.T.; Freed, L.E.; Guilak, F. A biomimetic three-dimensional woven composite scaffold for functional tissue engineering of cartilage. *Nat. Mater.* **2007**, *6*, 162–167. [[CrossRef](#)]
139. Lee, K.Y.; Mooney, D.J. Hydrogels for Tissue Engineering. *Chem. Rev.* **2001**, *101*, 1869–1880. [[CrossRef](#)]
140. Xue, B.; Tang, D.; Wu, X.; Xu, Z.; Gu, J.; Han, Y.; Zhu, Z.; Qin, M.; Zou, X.; Wang, W.; et al. Engineering hydrogels with homogeneous mechanical properties for controlling stem cell lineage specification. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2110961118. [[CrossRef](#)]
141. Zhao, Y.; Nakajima, T.; Yang, J.J.; Kurokawa, T.; Liu, J.; Lu, J.; Mizumoto, S.; Sugahara, K.; Kitamura, N.; Yasuda, K.; et al. Proteoglycans and Glycosaminoglycans Improve Toughness of Biocompatible Double Network Hydrogels. *Adv. Mater.* **2014**, *26*, 436–442. [[CrossRef](#)]
142. Yasuda, K.; Ping Gong, J.; Katsuyama, Y.; Nakayama, A.; Tanabe, Y.; Kondo, E.; Ueno, M.; Osada, Y. Biomechanical properties of high-toughness double network hydrogels. *Biomaterials* **2005**, *26*, 4468–4475. [[CrossRef](#)]
143. Liu, Y.; Wu, Y.; Zhou, L.; Wang, Z.; Dai, C.; Ning, C.; Tan, G. A Dual-Bonded Approach for Improving Hydrogel Implant Stability in Cartilage Defects. *Materials* **2017**, *10*, 191. [[CrossRef](#)]
144. Yang, Y.; Zhao, X.; Wang, S.; Zhang, Y.; Yang, A.; Cheng, Y.; Chen, X. Ultra-durable cell-free bioactive hydrogel with fast shape memory and on-demand drug release for cartilage regeneration. *Nat. Commun.* **2023**, *14*, 7771. [[CrossRef](#)]
145. Zhang, L.; Yan, H.; Zhou, J.; Zhao, Z.; Huang, J.; Chen, L.; Ru, Y.; Liu, M. High-Performance Organohydrogel Artificial Muscle with Compartmentalized Anisotropic Actuation Under Microdomain Confinement. *Adv. Mater.* **2023**, *35*, 2202193. [[CrossRef](#)] [[PubMed](#)]
146. Wang, J.; Wei, J.; Su, S.; Qiu, J.; Wang, S. Ion-linked double-network hydrogel with high toughness and stiffness. *J. Mater. Sci.* **2015**, *50*, 5458–5465. [[CrossRef](#)]
147. Zhang, S.; Li, Y.; Zhang, H.; Wang, G.; Wei, H.; Zhang, X.; Ma, N. Bioinspired Conductive Hydrogel with Ultrahigh Toughness and Stable Antiswelling Properties for Articular Cartilage Replacement. *ACS Mater. Lett.* **2021**, *3*, 807–814. [[CrossRef](#)]
148. Xue, B.; Gu, J.; Li, L.; Yu, W.; Yin, S.; Qin, M.; Jiang, Q.; Wang, W.; Cao, Y. Hydrogel tapes for fault-tolerant strong wet adhesion. *Nat. Commun.* **2021**, *12*, 7156. [[CrossRef](#)] [[PubMed](#)]
149. Freedman, B.R.; Uzun, O.; Luna, N.M.M.; Rock, A.; Clifford, C.; Stoler, E.; Östlund-Sholars, G.; Johnson, C.; Mooney, D.J. Degradable and Removable Tough Adhesive Hydrogels. *Adv. Mater.* **2021**, *33*, 2008553. [[CrossRef](#)] [[PubMed](#)]
150. Choi, S.; Moon, J.R.; Park, N.; Im, J.; Kim, Y.E.; Kim, J.-H.; Kim, J. Bone-Adhesive Anisotropic Tough Hydrogel Mimicking Tendon Entesis. *Adv. Mater.* **2023**, *35*, 2206207. [[CrossRef](#)] [[PubMed](#)]
151. Means, A.K.; Shrode, C.S.; Whitney, L.V.; Ehrhardt, D.A.; Grunlan, M.A. Double Network Hydrogels that Mimic the Modulus, Strength, and Lubricity of Cartilage. *Biomacromolecules* **2019**, *20*, 2034–2042. [[CrossRef](#)]
152. Zhao, Y.; Lo, C.-Y.; Ruan, L.; Pi, C.-H.; Kim, C.; Alsaied, Y.; Frenkel, I.; Rico, R.; Tsao, T.-C.; He, X. Somatosensory actuator based on stretchable conductive photothermally responsive hydrogel. *Sci. Robot.* **2021**, *6*, eabd5483. [[CrossRef](#)]
153. Hong, S.; Sycks, D.; Chan, H.F.; Lin, S.; Lopez, G.P.; Guilak, F.; Leong, K.W.; Zhao, X. 3D Printing of Highly Stretchable and Tough Hydrogels into Complex, Cellularized Structures. *Adv. Mater.* **2015**, *27*, 4035–4040. [[CrossRef](#)]
154. Zhou, Q.; Yang, K.; He, J.; Yang, H.; Zhang, X. A novel 3D-printable hydrogel with high mechanical strength and shape memory properties. *J. Mater. Chem. C* **2019**, *7*, 14913–14922. [[CrossRef](#)]
155. Yang, F.; Tadepalli, V.; Wiley, B.J. 3D Printing of a Double Network Hydrogel with a Compression Strength and Elastic Modulus Greater than those of Cartilage. *ACS Biomater. Sci. Eng.* **2017**, *3*, 863–869. [[CrossRef](#)] [[PubMed](#)]
156. Du, C.; Hu, J.; Wu, X.; Shi, H.; Yu, H.C.; Qian, J.; Yin, J.; Gao, C.; Wu, Z.L.; Zheng, Q. 3D printing of a tough double-network hydrogel and its use as a scaffold to construct a tissue-like hydrogel composite. *J. Mater. Chem. B* **2022**, *10*, 468–476. [[CrossRef](#)] [[PubMed](#)]
157. 3D-Printed Hydrogel Technologies for Tissue-Engineered Heart Valves. *3D Print. Addit. Manuf.* **2014**, *1*, 122–136. [[CrossRef](#)]
158. Heo, D.N.; Castro, N.J.; Lee, S.-J.; Noh, H.; Zhu, W.; Zhang, L.G. Enhanced bone tissue regeneration using a 3D printed microstructure incorporated with a hybrid nano hydrogel. *Nanoscale* **2017**, *9*, 5055–5062. [[CrossRef](#)] [[PubMed](#)]
159. Wallin, T.J.; Simonsen, L.-E.; Pan, W.; Wang, K.; Giannelis, E.; Shepherd, R.F.; Mengüç, Y. 3D printable tough silicone double networks. *Nat. Commun.* **2020**, *11*, 4000. [[CrossRef](#)] [[PubMed](#)]
160. Chu, Y.; Huang, L.; Hao, W.; Zhao, T.; Zhao, H.; Yang, W.; Xie, X.; Qian, L.; Chen, Y.; Dai, J. Long-term stability, high strength, and 3D printable alginate hydrogel for cartilage tissue engineering application. *Biomed. Mater.* **2021**, *16*, 064102. [[CrossRef](#)] [[PubMed](#)]

161. Choi, S.; Lee, K.Y.; Kim, S.L.; MacQueen, L.A.; Chang, H.; Zimmerman, J.F.; Jin, Q.; Peters, M.M.; Ardoña, H.A.M.; Liu, X.; et al. Fibre-infused gel scaffolds guide cardiomyocyte alignment in 3D-printed ventricles. *Nat. Mater.* **2023**, *22*, 1039–1046. [[CrossRef](#)] [[PubMed](#)]
162. Zhu, T.; Ni, Y.; Biesold, G.M.; Cheng, Y.; Ge, M.; Li, H.; Huang, J.; Lin, Z.; Lai, Y. Recent advances in conductive hydrogels: Classifications, properties, and applications. *Chem. Soc. Rev.* **2023**, *52*, 473–509. [[CrossRef](#)]
163. Zhang, L.M.; He, Y.; Cheng, S.; Sheng, H.; Dai, K.; Zheng, W.J.; Wang, M.X.; Chen, Z.S.; Chen, Y.M.; Suo, Z. Self-Healing, Adhesive, and Highly Stretchable Ionogel as a Strain Sensor for Extremely Large Deformation. *Small* **2019**, *15*, 1804651. [[CrossRef](#)] [[PubMed](#)]
164. Li, T.; Wang, Y.; Li, S.; Liu, X.; Sun, J. Mechanically Robust, Elastic, and Healable Ionogels for Highly Sensitive Ultra-Durable Ionic Skins. *Adv. Mater.* **2020**, *32*, 2002706. [[CrossRef](#)] [[PubMed](#)]
165. Yiming, B.; Guo, X.; Ali, N.; Zhang, N.; Zhang, X.; Han, Z.; Lu, Y.; Wu, Z.; Fan, X.; Jia, Z.; et al. Ambiently and Mechanically Stable Ionogels for Soft Ionotronics. *Adv. Funct. Mater.* **2021**, *31*, 2102773. [[CrossRef](#)]
166. Lu, Y.; Yang, G.; Wang, S.; Zhang, Y.; Jian, Y.; He, L.; Yu, T.; Luo, H.; Kong, D.; Xianyu, Y.; et al. Stretchable graphene–hydrogel interfaces for wearable and implantable bioelectronics. *Nat. Electron.* **2023**, *7*, 51–65. [[CrossRef](#)]
167. Leng, Z.; Zhu, P.; Wang, X.; Wang, Y.; Li, P.; Huang, W.; Li, B.; Jin, R.; Han, N.; Wu, J.; et al. Sebum-Membrane-Inspired Protein-Based Bioprotonic Hydrogel for Artificial Skin and Human-Machine Merging Interface. *Adv. Funct. Mater.* **2023**, *33*, 2211056. [[CrossRef](#)]
168. Zhang, W.; Wang, P.-L.; Huang, L.-Z.; Guo, W.-Y.; Zhao, J.; Ma, M.-G. A stretchable, environmentally tolerant, and photoactive liquid metal/MXene hydrogel for high performance temperature monitoring, human motion detection and self-powered application. *Nano Energy* **2023**, *117*, 108875. [[CrossRef](#)]
169. Bai, Z.; Wang, X.; Zheng, M.; Yue, O.; Huang, M.; Zou, X.; Cui, B.; Xie, L.; Dong, S.; Shang, J.; et al. Mechanically Robust and Transparent Organohydrogel-Based E-Skin Nanoengineered from Natural Skin. *Adv. Funct. Mater.* **2023**, *33*, 2212856. [[CrossRef](#)]
170. Zhang, Y.-Z.; Lee, K.H.; Anjum, D.H.; Sougrat, R.; Jiang, Q.; Kim, H.; Alshareef, H.N. MXenes stretch hydrogel sensor performance to new limits. *Sci. Adv.* **2018**, *4*, eaat0098. [[CrossRef](#)]
171. Xue, B.; Sheng, H.; Li, Y.; Li, L.; Di, W.; Xu, Z.; Ma, L.; Wang, X.; Jiang, H.; Qin, M.; et al. Stretchable and self-healable hydrogel artificial skin. *Natl. Sci. Rev.* **2022**, *9*, nwab147. [[CrossRef](#)]
172. Ji, D.; Park, J.M.; Oh, M.S.; Nguyen, T.L.; Shin, H.; Kim, J.S.; Kim, D.; Park, H.S.; Kim, J. Superstrong, superstiff, and conductive alginate hydrogels. *Nat. Commun.* **2022**, *13*, 3019. [[CrossRef](#)]
173. Li, H.; Lv, T.; Sun, H.; Qian, G.; Li, N.; Yao, Y.; Chen, T. Ultrastretchable and superior healable supercapacitors based on a double cross-linked hydrogel electrolyte. *Nat. Commun.* **2019**, *10*, 536. [[CrossRef](#)]
174. Yuk, H.; Wu, J.; Zhao, X. Hydrogel interfaces for merging humans and machines. *Nat. Rev. Mater.* **2022**, *7*, 935–952. [[CrossRef](#)]
175. Yu, Y.; Feng, Y.; Liu, F.; Wang, H.; Yu, H.; Dai, K.; Zheng, G.; Feng, W. Carbon Dots-Based Ultrastretchable and Conductive Hydrogels for High-Performance Tactile Sensors and Self-Powered Electronic Skin. *Small* **2023**, *19*, 2204365. [[CrossRef](#)] [[PubMed](#)]
176. He, H.; Li, H.; Pu, A.; Li, W.; Ban, K.; Xu, L. Hybrid assembly of polymeric nanofiber network for robust and electronically conductive hydrogels. *Nat. Commun.* **2023**, *14*, 759. [[CrossRef](#)] [[PubMed](#)]
177. Chong, J.; Sung, C.; Nam, K.S.; Kang, T.; Kim, H.; Lee, H.; Park, H.; Park, S.; Kang, J. Highly conductive tissue-like hydrogel interface through template-directed assembly. *Nat. Commun.* **2023**, *14*, 2206. [[CrossRef](#)] [[PubMed](#)]
178. Zhou, T.; Yuk, H.; Hu, F.; Wu, J.; Tian, F.; Roh, H.; Shen, Z.; Gu, G.; Xu, J.; Lu, B.; et al. 3D printable high-performance conducting polymer hydrogel for all-hydrogel bioelectronic interfaces. *Nat. Mater.* **2023**, *22*, 895–902. [[CrossRef](#)] [[PubMed](#)]
179. Chen, P.-Y.; Dorval Courchesne, N.-M.; Hyder, M.N.; Qi, J.; Belcher, A.M.; Hammond, P.T. Carbon nanotube–polyaniline core–shell nanostructured hydrogel for electrochemical energy storage. *RSC Adv.* **2015**, *5*, 37970–37977. [[CrossRef](#)]
180. Shi, Y.; Peng, L.; Yu, G. Nanostructured conducting polymer hydrogels for energy storage applications. *Nanoscale* **2015**, *7*, 12796–12806. [[CrossRef](#)] [[PubMed](#)]
181. Wang, Z.; Li, H.; Tang, Z.; Liu, Z.; Ruan, Z.; Ma, L.; Yang, Q.; Wang, D.; Zhi, C. Hydrogel Electrolytes for Flexible Aqueous Energy Storage Devices. *Adv. Funct. Mater.* **2018**, *28*, 1804560. [[CrossRef](#)]
182. Chan, C.Y.; Wang, Z.; Jia, H.; Ng, P.F.; Chow, L.; Fei, B. Recent advances of hydrogel electrolytes in flexible energy storage devices. *J. Mater. Chem. A* **2021**, *9*, 2043–2069. [[CrossRef](#)]
183. Liu, Z.; Liang, G.; Zhan, Y.; Li, H.; Wang, Z.; Ma, L.; Wang, Y.; Niu, X.; Zhi, C. A soft yet device-level dynamically super-tough supercapacitor enabled by an energy-dissipative dual-crosslinked hydrogel electrolyte. *Nano Energy* **2019**, *58*, 732–742. [[CrossRef](#)]
184. Li, L.; Zhang, Y.; Lu, H.; Wang, Y.; Xu, J.; Zhu, J.; Zhang, C.; Liu, T. Cryopolymerization enables anisotropic polyaniline hybrid hydrogels with superelasticity and highly deformation-tolerant electrochemical energy storage. *Nat. Commun.* **2020**, *11*, 62. [[CrossRef](#)] [[PubMed](#)]
185. Zeng, J.; Dong, L.; Sha, W.; Wei, L.; Guo, X. Highly stretchable, compressible and arbitrarily deformable all-hydrogel soft supercapacitors. *Chem. Eng. J.* **2020**, *383*, 123098. [[CrossRef](#)]
186. Fang, L.; Cai, Z.; Ding, Z.; Chen, T.; Zhang, J.; Chen, F.; Shen, J.; Chen, F.; Li, R.; Zhou, X.; et al. Skin-Inspired Surface-Microstructured Tough Hydrogel Electrolytes for Stretchable Supercapacitors. *ACS Appl. Mater. Interfaces* **2019**, *11*, 21895–21903. [[CrossRef](#)] [[PubMed](#)]
187. Wegst, U.G.K.; Bai, H.; Saiz, E.; Tomsia, A.P.; Ritchie, R.O. Bioinspired structural materials. *Nat. Mater.* **2015**, *14*, 23–36. [[CrossRef](#)] [[PubMed](#)]
188. Katti, K.S.; Katti, D.R. Why is nacre so tough and strong? *Mater. Sci. Eng. C* **2006**, *26*, 1317–1324. [[CrossRef](#)]

189. Lewis, R.V. Spider Silk: Ancient Ideas for New Biomaterials. *Chem. Rev.* **2006**, *106*, 3762–3774. [[CrossRef](#)] [[PubMed](#)]
190. Porter, D.; Guan, J.; Vollrath, F. Spider Silk: Super Material or Thin Fibre? *Adv. Mater.* **2013**, *25*, 1275–1279. [[CrossRef](#)] [[PubMed](#)]
191. Katiyar, N.K.; Goel, G.; Hawi, S.; Goel, S. Nature-inspired materials: Emerging trends and prospects. *NPG Asia Mater.* **2021**, *13*, 56. [[CrossRef](#)]
192. Chan, N.J.-A.; Gu, D.; Tan, S.; Fu, Q.; Pattison, T.G.; O'Connor, A.J.; Qiao, G.G. Spider-silk inspired polymeric networks by harnessing the mechanical potential of  $\beta$ -sheets through network guided assembly. *Nat. Commun.* **2020**, *11*, 1630. [[CrossRef](#)]
193. Gu, L.; Jiang, Y.; Hu, J. Scalable Spider-Silk-Like Supertough Fibers using a Pseudoprotein Polymer. *Adv. Mater.* **2019**, *31*, 1904311. [[CrossRef](#)] [[PubMed](#)]
194. Wang, J.; Cheng, Q.; Tang, Z. Layered nanocomposites inspired by the structure and mechanical properties of nacre. *Chem. Soc. Rev.* **2012**, *41*, 1111–1129. [[CrossRef](#)]
195. Dou, Y.; Wang, Z.-P.; He, W.; Jia, T.; Liu, Z.; Sun, P.; Wen, K.; Gao, E.; Zhou, X.; Hu, X.; et al. Artificial spider silk from ion-doped and twisted core-sheath hydrogel fibres. *Nat. Commun.* **2019**, *10*, 5293. [[CrossRef](#)]
196. Fu, F.; Chen, Z.; Zhao, Z.; Wang, H.; Shang, L.; Gu, Z.; Zhao, Y. Bio-inspired self-healing structural color hydrogel. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 5900–5905. [[CrossRef](#)] [[PubMed](#)]
197. Zheng, S.; Huang, R.; Lin, R.; Liu, Z. A phase field solution for modelling hyperelastic material and hydrogel fracture in ABAQUS. *Eng. Fract. Mech.* **2022**, *276*, 108894. [[CrossRef](#)]
198. Zhang, M.; Zhang, D.; Chen, H.; Zhang, Y.; Liu, Y.; Ren, B.; Zheng, J. A multiscale polymerization framework towards network structure and fracture of double-network hydrogels. *NPJ Comput. Mater.* **2021**, *7*, 39. [[CrossRef](#)]
199. Liu, H.; Du, C.; Liao, L.; Zhang, H.; Zhou, H.; Zhou, W.; Ren, T.; Sun, Z.; Lu, Y.; Nie, Z.; et al. Approaching intrinsic dynamics of MXenes hybrid hydrogel for 3D printed multimodal intelligent devices with ultrahigh superelasticity and temperature sensitivity. *Nat. Commun.* **2022**, *13*, 3420. [[CrossRef](#)]
200. Castro, A.P.G.; Yao, J.; Battisti, T.; Lacroix, D. Poroelastic Modeling of Highly Hydrated Collagen Hydrogels: Experimental Results vs. Numerical Simulation With Custom and Commercial Finite Element Solvers. *Front. Bioeng. Biotechnol.* **2018**, *6*, 142. [[CrossRef](#)]
201. Roy, J.K.; Pinto, H.P.; Leszczynski, J. Interaction of epoxy-based hydrogels and water: A molecular dynamics simulation study. *J. Mol. Graph. Model.* **2021**, *106*, 107915. [[CrossRef](#)]
202. Angelerou, M.G.F.; Frederix, P.W.J.M.; Wallace, M.; Yang, B.; Rodger, A.; Adams, D.J.; Marlow, M.; Zelzer, M. Supramolecular Nucleoside-Based Gel: Molecular Dynamics Simulation and Characterization of Its Nanoarchitecture and Self-Assembly Mechanism. *Langmuir* **2018**, *34*, 6912–6921. [[CrossRef](#)]
203. Ou, X.; Xue, B.; Lao, Y.; Wutthinitikornkit, Y.; Tian, R.; Zou, A.; Yang, L.; Wang, W.; Cao, Y.; Li, J. Structure and sequence features of mussel adhesive protein lead to its salt-tolerant adhesion ability. *Sci. Adv.* **2020**, *6*, eabb7620. [[CrossRef](#)]
204. Guo, K.; Yang, Z.; Yu, C.-H.; Buehler, M.J. Artificial intelligence and machine learning in design of mechanical materials. *Mater. Horiz.* **2021**, *8*, 1153–1172. [[CrossRef](#)]
205. Sha, W.; Guo, Y.; Yuan, Q.; Tang, S.; Zhang, X.; Lu, S.; Guo, X.; Cao, Y.-C.; Cheng, S. Artificial Intelligence to Power the Future of Materials Science and Engineering. *Adv. Intell. Syst.* **2020**, *2*, 1900143. [[CrossRef](#)]
206. Huang, J.S.; Liew, J.X.; Ademiloye, A.S.; Liew, K.M. Artificial Intelligence in Materials Modeling and Design. *Arch. Comput. Methods Eng.* **2021**, *28*, 3399–3413. [[CrossRef](#)]
207. Nagahama, K.; Kimura, Y.; Takemoto, A. Living functional hydrogels generated by bioorthogonal cross-linking reactions of azide-modified cells with alkyne-modified polymers. *Nat. Commun.* **2018**, *9*, 2195. [[CrossRef](#)]
208. Liu, X.; Inda, M.E.; Lai, Y.; Lu, T.K.; Zhao, X. Engineered living hydrogels. *Adv. Mater.* **2022**, *34*, 2201326. [[CrossRef](#)] [[PubMed](#)]
209. Fu, F.; Shang, L.; Chen, Z.; Yu, Y.; Zhao, Y. Bioinspired living structural color hydrogels. *Sci. Robot.* **2018**, *3*, eaar8580. [[CrossRef](#)]
210. Liu, X.; Tang, T.-C.; Tham, E.; Yuk, H.; Lin, S.; Lu, T.K.; Zhao, X. Stretchable living materials and devices with hydrogel–elastomer hybrids hosting programmed cells. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 2200–2205. [[CrossRef](#)] [[PubMed](#)]
211. Chen, G.; Wang, F.; Zhang, X.; Shang, Y.; Zhao, Y. Living microecological hydrogels for wound healing. *Sci. Adv.* **2023**, *9*, eadg3478. [[CrossRef](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.