

A review on tough and sticky hydrogels

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Abstract In this review, we survey recent literature (2009–2013) on hydrogels that are mechanically tough and adhesive. The impact of published work and trends in the field are examined. We focus on design concepts, new materials, structures related to mechanical performance and adhesion properties. Besides hydrogels made of individual polymers, concepts developed to toughen hydrogels include interpenetrating and double networks, slide ring polymer gels, topological hydrogels, ionically cross-linked copolymer gels, nanocomposite polymer hydrogels, self-assembled microcomposite hydrogels, and combinations thereof. Hydrogels that are adhesive in addition to tough are also discussed. Adhesive properties, especially wet adhesion of hydrogels, are rare but needed for a variety of general technologies. Some of the most promising industrial applications are found in the areas of sensor and actuator technology, microfluidics, drug delivery and biomedical devices. The most recent accomplishments and creative approaches to making tough and sticky hydrogels are highlighted. This review concludes with perspectives for future directions, challenges and opportunities in a continuously changing world.

Keywords Tough · Hydrogel · Adhesion · Polymer · Cross-linking · Mechanical strength

Introduction

Robust hydrogels that combine high strength with stimuli-responsiveness, swelling–deswelling, liquid–gel transitions,

antimicrobial, shock-absorbing, self-healing shape-memory effects, and surface adhesion are promising for the development of several new technologies [1–4]. For example, liquid microlenses can be actuated by tough hydrogels that respond to light, temperature or an electric field [5, 6]. Other materials and devices that benefit from tough hydrogels include new sensors [7], microfluidic devices [8, 9], components of batteries, electrochemical devices and ultrafiltration membranes [4]. Hydrogels made from chemo-mechanical or other stimuli responsive polymers have been evaluated for sensors and actuators [10–12]. For use in sensors and actuators, the concept is based on a large and reversible volume change of the hydrogel that is induced by physical or chemical stimuli. These stimuli are able to convert chemical energy into mechanical work forth and back [13]. The resulting materials are sometimes described as “chemical valves.”

Commercial and biomedical applications include wound and surgical sealants [14, 15], self-regulating drug delivery depots [16], materials for bioseparations [17] and hydrogel platforms for cell growth or tissue engineering [8, 18]. For example, poor mechanical stability of hydrogel encapsulated cells hampers the viability and use. Polymer hydrogels with liquid–gel transitions have great potential in tissue engineering and drug delivery therapies owing to the fact that these hydrogels can be easily mixed with cells or drugs in the liquid state prior to injection and cross-linking [19]. Such hydrogels work most efficiently when maintaining high strength, ideally attached to the surrounding tissue followed by degradation after cargo delivery.

Most synthetic, tough hydrogels are not adhesive. Generally speaking, it appears that many adhesive properties are found by serendipity. Alternatively, specific design efforts via targeted biomimetic approaches have been taken. Compared to bulk adhesives, hydrogel adhesives offer better modulus matching to substrates and transport properties. Modulus matching between the hydrogel glue and a substrate can better avoid bond failure. The capability to adsorb

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and release molecules makes hydrogel adhesives unique for sensor, drug delivery and sealant applications.

Tough but flexible soft materials are required for adhering rubber to metal in motor mounts as well as bone to ligament in tissue repair [20–23]. Optically clear and tough hydrogel adhesives can be used for connecting fiber optic cables and optical components [24]. Hydrogels are needed for materials in microfluidic devices and microarrays including lab-on-a-chip fabrication [5]. Degradation into nontoxic products becomes important when designing hydrogels for disposable applications, including sensors [7, 24, 25], microfluidic constructs [8], drug delivery matrices [26–28], separations technology [29], wound care materials [30], surgical sealants [31–33] and other unmet medical needs that require permanent or reversible tissue adhesion [34].

First, we will highlight the most recent literature on tough hydrogels by focusing on design concepts, new materials chemistries, properties and applications. Afterward, we will review hydrogels that are both adhesive and tough. This combination of properties is rare and difficult to achieve within one material. Adhesive properties, especially wet adhesion, are critical for developing medical products. Intended commercial applications guide the materials design and synthesis. Thus the end product will determine property optimization efforts of researchers as well as the choice of measurement techniques, which vary significantly. Such goals mean that a hydrogel is often developed to serve a specific purpose not necessarily combine adhesive and tough properties.

Strategies and concepts developed to make tough hydrogels capable of large deformation include interpenetrating hydrogels, double networks [35], slide ring polymer gels [36], topological or tetra-PEG hydrogels [37], ionically cross-linked copolymers [38], nanocomposite polymer hydrogels [39–42], self-assembled microcomposite hydrogels and combinations thereof (Fig. 1). We will focus on literature published mostly between 2009 and 2013. Several earlier outstanding reviews are available on the concept of tough hydrogels [35–41] thus we will highlight these papers when discussing the individual concepts. For older literature, the reader is referred to previously published research and review articles that specialize on individual aspects of hydrogels [2–4]. For example, Myung et al. [43] have reviewed the progress made in the development and characterization of interpenetrating polymer networks starting from the pioneering work done in the 1960s to the more recently reported responsive and tough interpenetrating hydrogel systems [43]. Besides reviewing the literature, Myung et al. present a model hydrogel system that suggests template or partial template polymerization of the second network which significantly contributes to mechanical property enhancements. Naficy et al. [2] have presented an overview of robust polymer hydrogels by focusing on toughening mechanisms and mechanical performance.

Messing and Schmidt [3] reviewed responsive hydrogels with a focus on shape changing and actuating materials. Calvert [4] wrote a tutorial style review article on hydrogels for soft machines. From an educational perspective, Calvert's review is ideal for introducing students to tough hydrogels and their applications. Several other reviews exist on biomedical applications of hydrogels that are tough and also not so tough [44–47]. Hydrogels that can mimic the extracellular matrix are important for tissue engineering [48–51]. Since tough hydrogels represent a relatively new topic, experimental studies are available but more applications are yet to be found [4]. With this aspect in mind, we present ongoing design concepts, potential applications and new materials engineering efforts.

Tough hydrogels

On the following pages, we will focus on design concepts, new and tough hydrogel materials, structures related to mechanical performance and mechanical testing data when available. For deformation of a hydrogel material, in the ideal case, uniaxial compression and biaxial tension should give identical values. Compared to tensile testing measurements, compression experiments are easier to perform both in terms of sample preparation and actual testing. For example, slipping between the grips and wet samples presents practical difficulties. Since hydrogels are often tested in compression, sometimes in tension and sometimes in both, the values of stress at break are not always directly comparable when reported as nominal stress. Large strains applied in compression can expand the cross-section of a sample and, as a result, resistance of the material can appear exaggerated. Conversely, the cross-section of a sample may become smaller when applying nominal stress in tension. Therefore, whenever possible and where data are available, we will specify whether the mechanical testing data such as stresses at break are nominal values (i.e., force over initial cross section, engineering values) or true values (i.e., force over current cross section). We will also add information on the experimental geometry.

Current and potential applications for these materials are found in the areas of sensor and actuator technology, microfluidics, drug delivery, biomaterials and biomedical devices. Figure 2 summarizes some application areas with examples.

Interpenetrating and double network hydrogels

Double network hydrogels consist of two interpenetrating and covalently cross-linked polymer networks (Fig. 1a–c) [52]. Gong and co-workers first succeeded in synthesizing such double network hydrogels [35, 52]. These materials

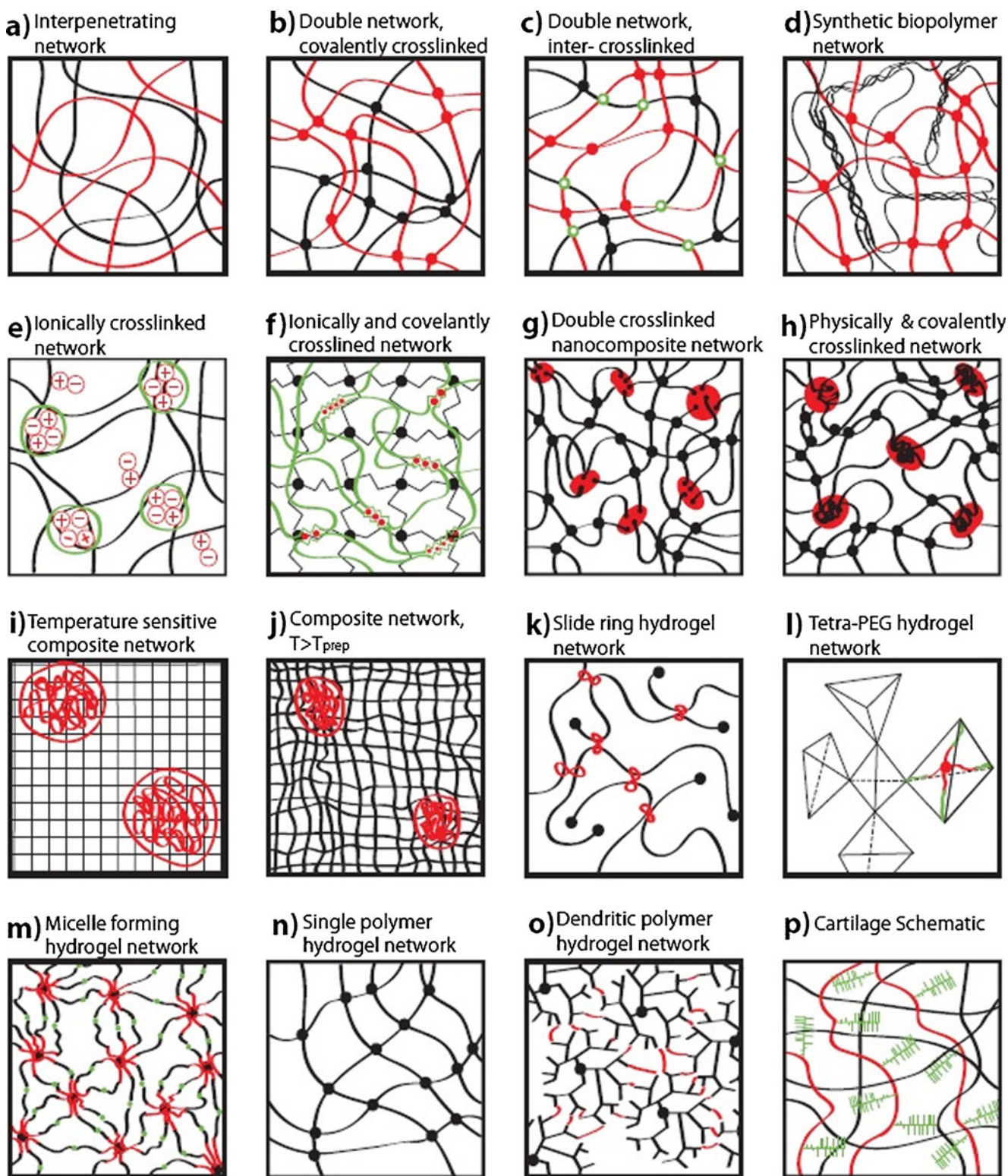
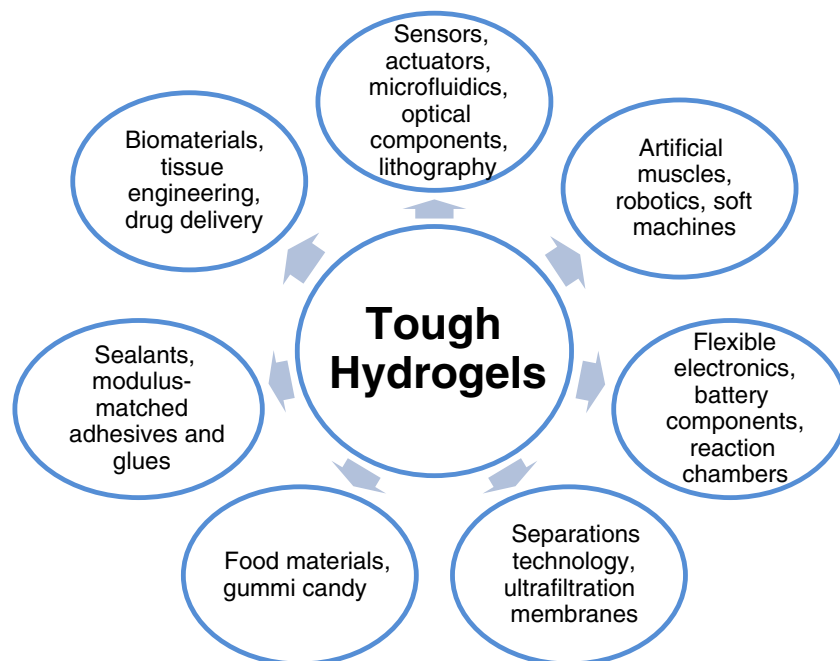


Fig. 1 Schematic representations of tough hydrogel network structures

display toughness and very high mechanical strength when compared to the individual polymer hydrogel controls [35]. The double networks are usually made by swelling a densely cross-linked network in a solution of a second monomer and

then polymerizing the second monomer to form a loosely cross-linked network. The first densely cross-linked network provides the hydrogel strength and the second loosely cross-linked network allows for energy dissipation at large strains.

Fig. 2 Application areas for tough hydrogels with specific examples



Both networks are sequentially polymerized but there is some cross-linking between the two networks possible, which is related to incomplete polymerization of the first network.

When such hydrogels are made from poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMPS) polyelectrolyte and linear polyacrylamide (PAAm) they may yield exceptional compressive strengths of ca. 20 MPa and fracture energies in the hundreds of J/m². Other hydrogel compositions from PAMPS and PAAm containing 90 % water are still capable of 17 MPa compressive strength (engineering definitions) [52].

Several theoretical studies that complement the experimental work suggest that double networks are tough owing to specific local yielding and hardening mechanisms take place during deformation [53]. For example, Brown [54] and then Webber et al. [55] expand on the Lake–Thomas and de Gennes theories. They report that when the first network breaks up to form many cracks, the second network can keep the overall system together, dissipate energy and cause shielding [54]. Tanaka [56] developed a phenomenological model that is similar to that of Brown [54]. These models account nicely for the high toughness observed in the double network hydrogels developed by Gong [35, 52]. The energy dissipation mechanism observed for the double network hydrogels is similar to the Mullins effect. This effect is a stress softening phenomenon observed under loading and characteristic for rubbers and other filled elastomers [55, 57]. Thus a disadvantage of the tough and double network gels is that, once covalent bonds are broken, the damage is irreversible. Above a critical stress, the first network fractures and builds clusters that can slide and act as cross linkers

to the second network [53]. These clusters present within the “used” gels have some similarity to the slide ring gels that we will discuss in a separate section below [58]. Here, toughening comes at the expense of irreversible failure of the first network.

Some other experimental and theoretical work that can be used to explain the toughness of double network hydrogels includes the neutron scattering work by Tirumala et al. [59], crack propagation studies by Baumberger et al. [60] and the soft–hard network model by Okumura [61]. Tirumala et al. [59] developed a molecular mechanism to explain hydrogel toughness by using neutron scattering techniques to determine periodic density fluctuations that resulted from large strains. Baumberger et al. [60] investigated crack dynamics in physical gels and the relation of solvent control and fracture to “viscoplastic chain pull-out.” Results from this work are important to optimizing hydrogel foods such as gummi candy, vitamin-containing gummies, aspic preparations as well as for biomaterials developments. For example, a water swollen gummi bear (candy) can be considered a tough hydrogel. Okumura [61] described a double network to be a heterogeneous material composed of “intertwined but energetically independent” soft and a hard networks. This model is then used to propose a mechanism for fracture energy and strength enhancement [61].

Since their discovery, several conceptual and material improvements have been made to double network hydrogels. For example, bacterial cellulose and gelatin were used to prepare tough double networks [35]. Microspheres containing double networks hydrogels and liquid crystalline double networks were both made [35]. These efforts, all by Gong’s group, are summarized in recent reviews article by Haque

et al. [35] and Gong [53]. The authors envision that these types of hydrogels will be most useful for biomaterials developments, specifically for load bearing applications including cartilage repair and regeneration [35].

Tough and electro-conducting hydrogels made of double networks are very attractive for developing artificial muscles, robotics, flexible electronics and soft actuators. The most desirable properties for these applications are soft and tough materials with flexibility, stretchability and electro-conductivity. Hydrogels may fulfill some of these requirements. Kishi et al. [62], reported on such hydrogels synthesized from electro-conductive poly 3,4-ethylenedioxythiophene (PEDOT) that was incorporated into a double network gel matrix. This double network hydrogel consisted of poly(2-acrylamide-2-methylpropane sulfonic acid) (PAMPS) and PAAm. The resulting “triple network” hydrogel made of PEDOT–PAMPS–PAAm was toughened by additional poly-ion complexation [62]. As a result, electronic conductivity and mechanical properties were enhanced significantly. Results from tensile testing experiments showed that fracture stresses of 1.4–2.1 MPa (engineering values) were achieved [62].

Several other research groups have used interpenetrating and double network concepts to synthesize tough hydrogels from a variety of different polymers combinations of polymers (Fig. 1a–c). For example, tough double network gels from poly(ethylene glycol)-diacrylate (PEG-DA) and poly(acrylic acid) (PAA) can be synthesized by sequential network formation using UV-initiated free radical polymerization [18, 43]. This procedure leads to an interpenetrating network where the PEG is densely cross-linked and the PAA is loosely cross-linked, with hydrogen bonding playing an important role in strain hardening. Some of the interpenetrating hydrogels may reach fracture stresses as high as 13 MPa (true values), as reported in a paper by Myung et al. [18, 43]. The hydrogels are transparent and have tunable mechanical properties that are most suitable for corneal implant applications [18, 43].

The synthesis of highly resilient and tough hydrogels has been reported by Cui et al. [63]. These hydrogels were made from thiol-norbornene used to end functionalize and then cross-link PEG and polydimethylsiloxane (PDMS). The fracture toughness of these materials was around 80 J/m² and the mechanical energy storage efficiency achieved was more than 97 % at strains up to 300 % [63]. The energy storage efficiency (i.e., resilience) of these hydrogels is comparable to that of natural materials such as resilin in dragonfly tendon (97 %) or elastin in skin (90 %). The authors state that the uniform network structure and the unstructured primary chains are critical in generating resilience and unique mechanical properties. Stress–strain curves obtained from tensile testing after repeated loading were identical, suggesting that the hydrogel network was not damaged. The Mullins effect was not observed. In a follow up paper

Cui et al. used the Voigt and Reuss models to describe and predict the elastic moduli of the hydrogels as function of composition. The Lake–Thomas theory was used to describe the fracture toughness of PEG-PDMS hydrogels having low volume fractions of PDMS [64]. For compression testing, true stresses were reported. For tensile testing, engineering values were reported [64].

Double networks can also be generated by repeatedly freezing and thawing hydrogels consisting of poly(vinyl alcohol) (PVA), PEG and water [65]. Zhang et al. [65] published work describing a very simple mix, freeze and thaw method to prepare tough PVA/PEG hydrogels. The freezing and thawing cycles initiate PVA crystallite formation and these crystallites physically cross-link the hydrogel network. The second PEG network was also partially crystallized and anchored to the PVA network. Hydrogels containing 90 % water were found to sustain compressive pressures as high as several MPa. Selected other hydrogel compositions were able to withstand compressive pressures around 15 MPa. Since these polymers are FDA approved, they are often considered for biomaterials synthesis. The hydrogels presented in this specific study are being used for sustained release drug delivery applications [65]. The authors show results from both tensile and compressive testing.

When star shaped poly(ethylene oxide–propylene oxide) (sPEOPO) polymer networks are cross-linked with PAAm for the second network, the resulting hydrogels are transparent, mechanically strong and partially self-healing [66]. Harrass et al. [66] reported compressive strengths of 5.6 MPa (engineering definitions) for samples with high water content and full recovery in loading–unloading experiments. The mechanical properties of these double network hydrogels were attributed to interactions between the two polymer networks and to partial healing of the first sPEOPO network after deformation. This healing capability is thought to be related to the presence of reversible hydrophobic interactions and to morphological characteristics. The authors envision these materials to be useful for load bearing biomedical applications such as cartilage repair. Recovery of these hydrogels allow repeated mechanical loading without a loss of mechanical strength [66].

A recent paper by Rakovsky et al. evaluated the mechanical properties of a interpenetrating double hydrogel system made from PEG and poly(methyl methacrylate) (PMMA) [67]. PEG, isophorone diisocyanate and glycerol were used for synthesizing the first network and methyl methacrylate, di(ethylene glycol) divinyl ether and dibenzoyl peroxide (initiator) provided the second network. A systematic study screened 27 resulting hydrogels of various compositions for the mechanical properties required in cartilage repair. Among these systems, several hydrogels were found to closely fit cartilage properties with regard to modulus, water

content and fatigue durability (e.g., 700 kPa cartilage is also found in human knee) [67].

Double network and interpenetrating hydrogels containing natural polymers

Scientists and engineers have been considering natural polymers when designing hydrogels for biomedical needs (Fig. 1). Besides cross-linking, the micro- and nanostructures of hydrogels, as well as the water content, often, but not always, correlate with mechanical properties. For example, photo-cross-linkable hyaluronic acid (HA) and semi-interpenetrating collagen have been used for generating tough hydrogels [68]. Compressive moduli of 800 kPa could be reached while the hydrogels maintained the biological properties of collagen and HA. This work was done by Brigham et al. [68], who envisioned that these materials might be used for fabricating microstructures, microchannels for soft lithographic techniques, matrices for cell encapsulation or tissue engineering, in general. Other interpenetrating polymer hydrogels have been prepared from gelatin and dextran that was functionalized with methacrylate and aldehyde [69]. Liu and Chan-Park [69] report compressive moduli in the range of 50 kPa and storage moduli around 10 kPa. These degradable hydrogel materials are seen promising for cell encapsulation and vascular tissue engineering [69].

In another study, DeKosky et al. [70] evaluated a tough and interpenetrating hydrogel made from agarose and PEG-DA to be used for cell encapsulation and cartilage tissue engineering. Briefly, agarose hydrogel samples prepared in phosphate-buffered solution (PBS) were soaked in PEG-DA monomer and then photo cross-linked. The resulting materials exhibited shear moduli of 40 kPa and compressive failure strains around 74 %. The experimental design was chosen based upon relevance to the target application and less on evaluating hydrogel toughness. A neo-Hookean model for ideal elastomers was used to evaluate and determine stress and strain values. For making a material that can potentially replace cartilage, compression-testing experiments are more relevant to materials characterization than, for example, tensile testing experiments [70].

Robust and semi-interpenetrating hydrogels made from poly(ethylene glycol) (PEG) and collagen consist of a primary covalently cross-linked PEG network with a secondary semi-interpenetrating and physically cross-linked collagen network [71]. Careful synthesis and formulation was necessary so as to maintain the bioactive properties of collagen while avoiding denaturation into gelatin. Non-covalent interactions between the two networks are expected with mechanical properties suggesting the presence of synergistic interactions between the two polymers. Collagen did not easily “dissolve” within the PEG network, but hydrogen bonding between the PEG and collagen may have led to

improved miscibility, which in return made the hydrogels translucent. Fracture stresses of 27–30 kPa could be achieved and elongations of ca. 300 % recorded (engineering values were given). This robust and model hydrogel system was designed to be an injectable matrix for viscoelastic tissue engineering [71].

Among the more creative approaches, Wang et al. [72] reported on an exotic version of a double network hydrogel. This group synthesized a tough material by combining fresh jellyfish gel and PAAm or polyacrylic acid. The synthesis was done by radiation-induced polymerization of a monomer-soaked jellyfish gel. Cross-linking took place without an additional cross-linking agent. Mechanical properties suggest that interactions between the two networks are present. Tensile testing showed that the materials reached elongations over 95 % without breaking (using the definitions of engineering stress and strain). Tensile stresses around 40 MPa were measured. Compressive testing data were equally impressive. The aim of this study was to evaluate how the original and well developed microstructure of jellyfish gel, which is already tough on its own, can be used for hydrogel synthesis. This concept and the results might generate knowledge about the influence of microstructures on tough hydrogel design [72].

Ionically cross-linked hydrogels made to be tough and elastomeric

Tough, resilient and self-healing materials can be developed by introducing covalent cross-linking to one network through reversible physical cross-linking (i.e., non-covalent) or by simply adding physical cross-linking. These bonds are complementary to covalent bonding within the polymer network. Examples include nanocomposite hydrogels, ionically cross-linked tough hydrogels and double cross-linked hydrogel versions (Fig. 1e). These hydrogels were developed to be models for testing either a basic hypothesis or to provide a proof of concept for when a specific application is in mind.

Tough, ionically cross-linked and self-assembled hydrogels can be made from cross-linking polyelectrolytes such as poly(methacrylate) and poly(methacrylic acid) triblock copolymers with divalent ions from Zn^{2+} , Ca^{2+} , Ni^{2+} , Co^{2+} and Cu^{2+} acetate solutions [38]. Mechanical properties of such hydrogels were found to depend strongly on the cation type and concentration. For example, cross-links between the polymer and Zn^{2+} ions were stronger than bonds between the polymer and Ca^{2+} ions. Overall, these hydrogel networks can mimic the structural characteristics and toughness of double network hydrogels although they do not have two interpenetrating networks. Instead, only one single polymer network is cross-linked twice. The polyelectrolyte midblock is ionically associated with other polyelectrolyte midblocks. The

triblock copolymer backbone is physically cross-linked through self-assembly, which is similar to the loosely cross-linked portion of a double network. The resulting materials can reach fracture stresses up to 1 MPa using engineering definitions [38].

A similar principle can be used to generate tough hydrogels by combining a covalently cross-linked PAAm network with a reversibly cross-linked alginate- Ca^{2+} network (Fig. 1f) [73, 74]. Within this type of double network, the ionic alginate- Ca^{2+} cross-links can be “unzipped” by deformation and then heal by “re-zipping” after deformation forces are removed. Thus the energy dissipated during material deformation is recoverable. Meanwhile the covalent bonding preserved the initial state of the network before and after stretching. Mechanical testing results showed that the gel could be stretched to >20 times its original length and retain high fracture energy. At rupture, the stress was 156 kPa and the final stretch length was 23 times the original lengths [74]. The concept of synthesizing nanocomposite hydrogels from polymers and charged nanoparticles provides another method of producing ionically cross-linked and high strength gels [39, 40, 73, 74].

Self-healing and tough hydrogels can be synthesized by copolymerizing stearyl methacrylate (C18) or dococyl acrylate (C22) with acrylamide in a micellar solution of sodium dodecyl sulfate (SDS) [75]. The monomers C18 and C22 are hydrophobic and the acrylamide is hydrophilic. Addition of salt (NaCl) allows for solubilization of the hydrophobic monomers within the SDS micelles, which is critical in producing tough hydrogels. The resulting materials can be dissolved in SDS solutions. The physical cross-linking appears to be responsible for this toughness. Fractured materials were repaired by simply bringing together the separated segments or cut joints to self-heal. After pressing the joints together, the samples could be extended to ca. 3,600 %, although the original length is not recoverable. With this system, Tuncaboylu et al. [75] have discovered a new hydrogel system with unusual and intriguing properties.

Elastomeric and salt-containing hydrogels can also be developed for sensor materials used in detecting large strains [76]. Here, large strain sensing refers to strains up to 25 %. Manandhar et al. [76] reported on such a hydrogel sensor that was made from a formulation containing polyetheramine mixed with PEG-diglycidyl ether in NaCl solution. The resulting hydrogel did not show hysteresis behavior as would be expected for other soft piezoresistors that are commonly used for large strain sensing. The sensing behavior of the hydrogel was found to depend on the deformation. The Young's modulus of the hydrogel elastomer was ca. 1 kPa, which is sufficient and desired for sensing applications. The hydrogels investigated by Manandhar et al. [76] can be used for making strain sensing textiles needed for rehabilitation, sports training and also for synthesizing hydrogel matrices

that allow studying how stem cells respond to strains. The specific hydrogel system investigated in this paper is evaluated for elastic strain sensing textiles as well as for monitoring the joint motions of robotic arms [76].

Self-healing hydrogels that are held together by only supramolecular forces, can be made mechanically strong. Wang et al. [77] reported on a supramolecular hydrogel system with elastic moduli around 0.5 MPa. This mouldable and thixotropic (i.e., shear thinning) hydrogel was prepared by simply mixing charged clay nanoparticles (Laponite) with PEG-based dendrimers used for molecular binders (Fig. 1-g,h). Such systems are physically cross-linked, self-healing and resist dissolution in water or other solvents. These materials can immobilize enzymes to preserve biological activity including that of myoglobin, thereby opening new biotechnology applications [77].

A combination of an ionically cross-linked, interpenetrating network and a nanocomposite hydrogel was reported by Lin et al. [78]. This tough material was made of PAA, Ca^{2+} alginate and silica nanoparticles which were added for reinforcement. The silica increased compressive strength of the hydrogel significantly and values of 9.7 MPa (engineering values) could be reached for a hydrogel containing 3 % PAA, 3 % alginate and 24 % silica. The compressive strength was calculated by force over initial area. This hydrogel system can provide a matrix for soft tissue engineering [78].

Another method for synthesizing tough polymer hydrogels is introducing charged nanoparticles to be multifunctional cross-linkers. For example, Laponite (LRD), is a synthetic silicate ($\text{Na}^{+}_{0.7}[(\text{Mg}_{5.5}\text{Li}_{0.3})\text{Si}_8\text{O}_{20}(\text{OH})_4]^{-0.7}$) shaped into nanoplatelets of ~25 nm diameter and ~1 nm thickness [79–81]. This material is also referred to as “synthetic clay” due to the similarity to natural clay. The polymer within such a hydrogel network affords both covalent cross-linking and physical cross-linking via interactions such as hydrogen bonding and ionic bonding. Cross-linking of the polymer to the nanoparticles can be covalent, non-covalent or both. The resulting materials are usually called “nanocomposite hydrogels.” These systems are most probably cross-linked by additional ionic interactions, thus they also qualify as ionically cross-linked hydrogels. Several good reviews have been published recently on this topic [2, 40, 82]. We will elaborate on the most common approaches below.

Tough nanocomposite (NC) polymer hydrogels

Tough NC polymer hydrogels (so-called “NC” gels) are made by radical polymerization of monomer solutions that contain exfoliated silicate nanoplatelets (clay). The initiator is adsorbed onto the nanoplatelet and polymerization then starts from these surfaces (Fig. 1g). After polymerization the polymer ends appear grafted onto the nanoplatelets and this

attachment is believed to be noncovalent in nature [82]. Since many polymer chains can attach to one nanoplatelet, the nanoparticles become multifunctional cross-linkers within the polymer network [39, 40, 83]. A variety of polymers and nanoparticle combinations have been explored and used for synthesis. One of the more extensively characterized hydrogel systems was that first developed by Haraguchi and Takehisa [39]. These nanocomposite hydrogels were made of *N*-iso-propylacrylamide, *N,N*-dimethylacrylamide or acrylamide polymers and silicate nanoplatelets (Laponite). Synthesis of the hydrogels usually requires the polymerization to be initiated from the silicate surfaces. Brush-like polymers then grow from the flat surfaces and connect several silicate nanoparticles thereby building up a cross-linked network (Fig. 1g,h). These hydrogels have elongations at break of at least 1,000 % [39, 82].

Since such hydrogels were first introduced [39], a great deal of additional research has been published in this area by the same group [82]. For example, Ren et al. [84] reported on the effects of counterions of Laponite platelets upon the swelling behavior of nanocomposite hydrogels [84]. The authors found that replacing various counter-ions associated with silicate surfaces for monovalent cations such as K^+ and Li^+ led to hydrogel swelling. By contrast, multivalent cations such as Ca^{2+} , Mg^{2+} , and Al^{3+} decreased hydrogel swelling. This effect was thought to correlate with interactions between Laponite clay platelets and multivalent cations [84]. Biocompatible tetra-PEG polymers and stimuli sensitive copolymers were also combined with Laponite to synthesize a variety of tough hydrogels of different structures and mechanical properties. Some of the resulting newer materials can reach fracture stresses larger 100 kPa, elongation values over 1,000 % as well as exhibit high tenacity. Bending and twisting could exceed more than 360° . Most of these findings are summarized in a review article by Haraguchi [82].

Covalently and physically cross-linked nanocomposite hydrogels

Covalently and physically cross-linked hydrogels are often termed as double cross-linked hydrogels (Fig. 1f–h). Several research groups have observed that the presence of network inhomogeneities and clusters of high cross-link densities decrease the strength of tough hydrogels [55, 85]. This trend might not apply to hydrogels that are both covalently and physically cross-linked. Multifunctional and reversible cross-linkers allow some mobility and dispersion of inhomogeneities and cross-linking densities during hydrogel stretching. Chain rearrangement is possible between the networks, which may reduce the number of defects [86]. Once strain is released, the material may then self-heal to a certain degree. Polymer can reversibly attach and detach to or from a charged nanoparticle within the constraints of a

covalently cross-linked network, and a tough nanocomposite polymer hydrogel may be obtained [86].

Covalently cross-linked polymers and non-covalently attached nanoparticles may be combined to yield a double cross-linked network that is conceptually, a hybrid of double network and ionically cross-linked hydrogels. Essentially, one single polymer network is cross-linked twice. For example, a double cross-linked nanocomposite hydrogel can be made from a photopolymerized PEG-diacrylate (PEG-DA) in the presence of charged silicate nanoplatelets (Laponite) [87]. The resulting hydrogel networks consist of (1) covalently cross-linked PEG-DA chains and (2) PEG chains that are non-covalently cross-linked to Laponite. This hydrogel system can be tough, bioactive, and surprisingly adhesive to surfaces [88]. More details on these sticky properties are discussed in the adhesive hydrogel section below.

A mechanism very similar to that found in the polymer–Laponite systems is observed with nanocomposite hydrogels made from PEG-DA and hydroxyapatite nanoparticles [89]. The resulting tough materials are highly extensible (2,000 %) and reach fracture stresses near 1 MPa (engineering values). Within a covalently cross-linked PEG network, the charged hydroxyapatite interacts with PEG through non-covalent interactions including ionic, dipole and hydrogen bonding schemes. The individual molecular interactions that lead to toughness within this specific hydrogel system are not yet known. However similarities are observed with a polymer–silica hydrogel system investigated by Lin et al. [90] and reviewed below. The covalent and non-covalent cross-linking bring about toughness and strength within the PEG-hydroxyapatite hydrogel while maintaining reversible compression and near fully recoverable elongation (2,000 %). These tough hydrogels have much in common with elastomers. The toughest samples are translucent to near opaque. Photo cross-linking reactants thus require thin samples and longer polymerization times. Since these materials have been discovered most recently [89], more work is needed to optimize mechanical properties. Potential applications are seen for drug delivery and tissue regeneration, especially within the context of orthopedic applications [89].

Lin et al. [90] have synthesized tough poly(*N,N*-dimethylacrylamide) (PDMA)-silica (Ludox SM30) nanoparticle hydrogels and characterized the mechanical properties in order to understand the physical interactions between silica and polymer. Incorporation of only 7 % (volume fraction) of silica nanoparticles in the hydrogel increased compression strength and fracture toughness significantly. Both compression testing and tensile testing experiments were done [90]. The experimentally obtained elastic moduli were compared to theoretical modulus calculations from the Guth–Gold model. This model can predict the elastic moduli of rubbery matrixes stuffed with weakly interacting particles. However, a lack of agreement with the model, confirmed the

prediction that the polymer is strongly adsorbed onto the silica nanoparticles. These nanoparticles are providing additional cross-link points to the network, thus stiffening the hydrogel. Strain-dependent hysteresis was observed but there appeared to be no permanent damage after repeated cycling. Recovery of strength was related to adsorption and desorption of polymer to the silica nanoparticles. When a polymer chain reaches its maximum extensibility just prior to desorption, strain hardening takes place. This strain hardening is related to the transition from entropic elasticity to enthalpic elasticity as seen in other network systems. The authors compare their experimental results with insights from theory. For example, compression testing experiments suggest that the Mullins effect is not observed with these hydrogels and the sample structure returns to their initial state after deformation. The fracture behavior, strength and toughness contradict the classic Lake–Thomas theoretical predictions for rubbery networks [91]. Although the hydrogel system presented in this study is not as tough as the double network hydrogels, the authors present a quantitative data analysis and interpretation. This work provides understanding of polymer nanoparticle adsorption processes and insights on the molecular origins related to high strain deformations and fracture properties. This report also provides good model systems for further studying nanoparticles within covalently cross-linked networks [90]. To summarize, this paper is worth highlighting and recommended for those who are interested in understanding why hydrogels are tough.

Double network hydrogels made from a PAMPS polyelectrolyte and linear PAAm may yield exceptional compressive strengths of ca. 20 MPa (engineering definitions) [35]. When silica nanoparticles are introduced into the polymer network, such hydrogels resist fracture up to 73 MPa (engineering definitions) [92]. Maximal reinforcement could be achieved by adding only 1 wt.% of vinyl modified silica nanoparticles (150 and 300 nm diameter). The authors (Wang et al.) explained that the fracture mechanism of these double network and nanocomposite hydrogels was based on previously reported yielding behavior [92].

Highly resilient and extensible hydrogels can also be synthesized from functionalized graphene sheets and polymers [93]. The graphene sheets provide multifunctional cross-linkers for the polymer network. When in situ grafting polymerization is used for synthesizing hydrogels from graphene peroxide and acrylamide monomers, exceptional properties such as tensile strengths of up to 1.2 MPa and elongations up to 5,300 % are achieved. Here the authors use engineering definitions of stress and strain. The new materials have exceptional properties. According to Liu et al. [93], these nanocomposite hydrogels have potential to be used in artificial tissue design as well as for development of biomimetic machines.

Microsphere reinforced tough composite hydrogels

Hydrogels can be mechanically reinforced through the addition of microspheres or microgels (Fig. 1i,j). Microgels are composed of spherical micrometer or nanometer large particles made from polymer hydrogels or porous polymers that are stimuli responsive. Microgels are not hydrogels themselves but properties of stimuli responsive microgels with adjusted functionalities can be transferred to the hydrogels [94]. While many research groups have published on the synthesis of microsphere or microgel reinforced hydrogels, detailed mechanical properties are not always reported. Instead, papers tend to describe structures and properties for fundamental concepts, solving specific problems, discussing hypotheses or developing products. Below we review the most recent developments and highlight some creative ideas.

When microspheres made from tough hydrogels are functionalized and then covalently cross-linked the original microgel becomes a toughened hydrogel composite. Huang et al. [95] synthesized such a material from rigid microspheres and a soft polymer. Emulsion polymerization was used to prepare microspheres from styrene, butyl acrylate and acrylic acid. Then oxygen and γ -irradiation introduced peroxides onto the microsphere surfaces. The activated microspheres were dispersed into an acrylic acid monomer solution. Polymerization started from the sphere surfaces. As such the microspheres provided multifunctional cross-linking. A conceptual analogy can be drawn to nanocomposite hydrogels made from silicate nanoplatelets that are attached to several polymer chains. The scope of hydrogel microgel composites has been expanding, to include a variety of different particles and polymers such as poly(*N*-isopropylacrylamide-co-acrylic acid) (P(NIPAM-co-AAc)) [96]. As the temperature of these gels is changed, significant volume changes were observed. Consequently, stimulus-responsive applications including sensors, actuators and bioseparation devices come to mind readily [96].

Core-shell microgels (microspheres) can be made into double network hydrogels by using a poly(*N*-isopropylacrylamide) core and a poly(vinyl amine) shell [97]. Graft copolymerization from the microsphere surfaces, of acrylic acid, acryloyloxyethyl trimethyl ammonium chloride, and acrylamide yielded hydrogels. These systems were comprised of a cross-linked ungrafted polymer for the first network and a grafted microgel for the second network. Compressive strengths were found to be around 17–30 MPa (engineering definitions) [97].

Other microgel reinforced hydrogels with high strength and toughness were published by Hu et al. [98]. Toughness was fine-tuned by changing the microgel composition [98]. These microgel-containing hydrogels are double networks made of a loosely cross-linked PAAm network and a densely cross-linked polyelectrolyte microgel network. The polyelectrolyte

consists of poly(2-acrylamido-2-methyl propanesulfonic sodium) microspheres [98]. Mechanical strength and toughness of these microsphere-reinforced materials depended on the formulation techniques and were comparable to other double network hydrogels synthesized by Gong's group [35]. Applications for such hydrogels are expected in the general biomedical area. Similar microgel reinforced hydrogels were published by Qin et al. [94], who used new chemistries to generate reactive microgels that can be cross-linked into a hydrogel.

Composite hydrogels synthesized from a PAAm matrix and thermosensitive poly(*N*-isopropylacrylamide) (PNiAAm) microgel beads have enhanced mechanical properties relative to single polymer controls due to physical cross-linking between the two polymers [99]. High temperatures further increase mechanical properties for certain hydrogel compositions. Using cavitation rheology the highest stress at break achieved was 3,500 Pa and the highest strain at break was found around 130 % [99]. Synthetic procedures can be optimized to retain full responsiveness of the micro beads while not affecting the macroscopic dimensions of the overall hydrogel [100]. These materials can be useful model systems for studying tracer diffusion in different environments. For example, Lehman et al. [101] investigated formation of stimuli responsive and interpenetrating networks inside microgel beads and the mobility of dextran tracers throughout these beads. The authors found that beads collapse upon heating. These materials are promising for applications that require membranes with tunable permeability including sustained release drug delivery or separations devices. This type of hydrogel has potential to be a general model system for studying the dynamics of drugs, growth factors, signaling molecules and other additives within cell-laden hydrogels [99, 101].

Slide ring hydrogels

“Slip-link” or slide ring polymer hydrogels are topological materials made from necklace-like macromolecules (Fig. 1k) [58]. These gels have been compared to pulleys and chains with knots. Movable, cyclic cross-links can slide along a polymer chain and thus allow for extensive stretching. Chain ends have stopper molecules (topological restrictions) that prevent dissociation of the cyclic molecules from the axis. The cyclic molecules are polyrotaxane or catenane rings that can be chemically modified to better suit a specific application [102]. For example, maltose attached to rings may interact with sugar binding proteins. Polyrotaxanes modified with cationic oligomers or mesogens can be used for gene delivery and liquid crystal applications [58]. In another example, α -cyclodextrin rings were threaded onto linear polymer such as PEG and some of the rings were cross-linked to cyclodextrin threaded on different chains [103, 104]. The resulting cross-linking junctions are shaped like a figure

eight. Two different polymer chains are connected but the junctions can move freely along the two chain axes within the polymer network. When the sample is stretched, entropy loss from the polymer deformation then transfers to that of the free cyclic molecules that are heterogeneously distributed. The Young's moduli of these slide ring gels are not proportional to the cross-linker concentration, as one might expect for a rubber-like and covalently cross-linked network. Extensibility of these materials can be very high and elongations at break are found to be around 1,000 % [58]. The hydrogel is capable of swelling to ca. 500 times its original weight [58]. The mechanics of slide ring gels differ from the traditional polymer networks in that there is a “sliding state” where polymer chains are actively sliding through the links. This phenomenon accounts for the marked differences in mechanical properties. Based on the concept of slide-ring gels, the authors mention that bulk slide-ring elastomers with scratch proof properties have been developed [58].

Tough tetra-PEG hydrogels

Tetra-PEG hydrogels can be made from tetra-PEG macromers containing functional groups such as amines and esters (Fig. 1) [37, 105]. These hydrogels are a different and unique class of tough materials. Trapped entanglements are almost completely absent. Network defects are also negligible [41]. Mechanical testing and scattering experiments suggest that the hydrogels consist of elastic polymer “blobs” (i.e., coils) that are packed within the gels. For example cross-end coupling of tetra-amine-terminated PEG and tetra-*N*-hydroxysuccinimide-glutaraldehyde-terminated PEG leads to hydrogel networks with high cross-linking efficiency and little hysteresis. This behavior is very similar to that of an elastic rubber. Scattering studies show that these tetra-PEG hydrogels are mostly homogeneous with low concentration fluctuations comparable to those of the corresponding solutions [37, 105]. Concentration fluctuations are changes in density within the same hydrogel. When the ratio of the reacting macromonomers is not stoichiometric, heterogeneity will develop, owing to increases in structural defects [106, 107]. The maximum compression strength of the toughest hydrogels of this type was reported to be around 2.5 MPa (The stress strain curves were fitted using an inverse Langevin function model) [41].

Other tough hydrogels with novel microstructures and uses

PAAm-based hydrogels can be prepared by micellar copolymerization of acrylamide monomers and *N,N*-methylenebis(acrylamide) in the presence of hydrophobic comonomers such as *N*-butyl-, *N*-hexyl-, *N*-octyl-, or *N,N*-dihexylacrylamides [108]. The resulting PAAm hydrogels could be extended to ca. 300 % elongation ratios. The toughest of these gels could reach fracture stresses up to 80 kPa (engineering definitions)

[108]. The toughness observed was related to the presence of temporary associations of hydrophobic blocks within the micellar hydrogel network (Fig. 1m). Abdurrahmanoglu et al. [108] see potential applications for these hydrogels in the general area of soft materials.

Friedrich et al. [109] reported on another tough hydrogel system made by copolymerizing thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAAm) with cationic surfactant monomers. Polymerization was carried out in an aqueous micellar solution using γ radiation. The two surfactants used were 11-(acryloyloxy)undecyl) trimethylammonium bromide and (2-(methacryloyl)ethyl) dodecyldimethylammonium bromide [109]. The hydrogels displayed improved mechanical properties that were explained in terms of additional cross-linking by copolymerized micelles. When elongated, selected hydrogels could resist 6-fold stresses when compared to controls. Elongational flow measurements indicated that copolymerization with cationic surfactant monomers leads to increases in ductility and decreases in stiffness [109]. This paper summarizes fundamental research aimed at understanding the properties of responsive hydrogels.

Injectable PNIPAAm-PEG hydrogels have been investigated for use in load-bearing nucleus pulposus replacement [110]. Nucleus pulposus is a soft and gelatinous substance of cross-linked collagen in the middle of the intervertebral disc. Thermosensitive PNIPAAm displays a lower critical solution temperature (LCST ~ 32 °C), allowing injection of low viscosity solutions at room temperature. Once injected, the solution solidifies and a tough hydrogel is formed at body temperature, above the LCST. During synthesis, when PEG is grafted, care must be taken so as not to change this LCST. Thomas et al. reported on the synthesis of such a grafted and branched PNIPAAm-PEG network that was developed specifically for nucleus pulposus replacement [110]. Addition of grafted PEG reduced the compressive modulus but enhanced dimensional recovery of the hydrogel materials. Fast recovery is critical to function when the hydrogel is to be used for repair of an intervertebral disc [110].

Adhesive and tough hydrogels for sealants and glues

Bonding two substrates together requires both adhesive interactions with surfaces as well as cohesive bonding within the bulk material. Cohesive molecular interactions lead to the inner strength of a glue. Surface adhesion depends upon interactions between glue and substrate. When adhesion and cohesion are balanced, glue functions well [20–22]. Here we review literature on new tough and adhesive hydrogel systems. Wherever known, molecular interactions contributing to adhesive and cohesive bonding will be described and adhesion data presented.

Most synthetic tough hydrogels are not adhesive and only a modest amount of literature is available on adhesive

hydrogels. Systems that are adhesive are not always described to be tough or robust thereby complicating literature surveys. Making comparisons between different studies can be at times challenging. Differences in substrate type (e.g., metal, skin, plastic), substrate treatment (e.g., wet, moist or dry), curing time, polymerization before attaching to the substrate versus photo-cross-linking to the substrate surface and measurement techniques (e.g., lap shear, peel test, burst pressure tests) among several other parameters mean that direct quantitative correlations cannot easily be drawn [22]. New methods are being developed that can measure shear strength of adhesive hydrogels that are in limited supply [111]. Here, we will highlight new adhesive hydrogel systems and present adhesion data, when available. Current and potential applications of adhesive hydrogels are also listed as they appear in the reviewed papers. These applications and selected examples are summarized in Fig. 3.

Dendritic polymer hydrogel adhesives

Several dendritic and PEG-based hydrogel sealants have been developed for biomedical uses (Fig. 1o). Among these, Grinstaff et al. described creative ways to make adhesive hydrogels from dendritic polymers [112–114]. These materials can be used for repairing and sealing corneal wounds as well as cartilage [114]. Generation of reaction chambers for high-throughput screening of molecular recognition events even appears to be possible [114]. The hydrogels are made from peptide dendrons (e.g., Lys₃Cys₄) with different types of bifunctional and aldehyde-terminated PEG macromers, with propione aldehyde, butyraldehyde, and 2-oxoethyl succinate functionalities [113]. The cross-linking techniques used when generating these materials are based upon photochemistry and chemical ligation. Photochemical cross-linking is adaptable to endoscope-assisted microsurgery. The relevant electrophile–nucleophile cross-linking chemistries do not need light but do require careful timing and placement onto the substrate [114]. Once polymerized atop surfaces, the resulting hydrogels have adhesive strength values ranging from 13 to 700 kPa for polymer compositions ranging between 10 % and 50 % of polymer and the rest is water [113, 114].

Wet and moist adhesive hydrogels based on DOPA chemistry

A particularly intriguing class of adhesives uses the chemistry of marine mussels. Key to adhesion of these shellfish is a class of proteins containing 3,4-dihydroxyphenylalanine (DOPA) amino acids. By introducing this biochemistry to hydrogels, wet setting glues can be made. With DOPA, dopamine or other derivatives of catechol (3,4-dihydroxybenzene), irreversible cross-linking is possible via oxidation and metal

Fig. 3 Some application areas of adhesive hydrogels and specific examples



chelation mechanisms [115–118]. Since many adhesives used in technological and biomedical applications require soft materials that perform well in wet environments, there is a great need for wet setting hydrogel sealants and glues. For example, tissue specific applications may require a hydrogel to have unique toughness and adhesive properties [119]. A variety of hydrogels have been developed using DOPA and catechol chemistry, most of which have comparable adhesion values when tested under similar conditions. Introducing mussel chemistry may help bring adhesion to hydrogels and other wet environments, where bonding tends to be quite difficult.

Hydrogel sealants synthesized by Brubaker et al. were made from a branched PEG that was modified with elastase and DOPA [33, 120]. These hydrogels are wet adhesive, enzyme degradable and envisioned for sealing human fetal membrane defects after prenatal surgery [121], attaching transplanted islets to tissue surfaces in order to reverse diabetes [120] and for general surgical wound closure [122]. The storage moduli for these hydrogels were ~10 kPa and strain at failure exceeded 200 % strain. The main shear strength measured for these hydrogel adhesives was in the range of 30 kPa [33]. These numbers were obtained from lap shear testing of wet porcine dermis. All bonded pig skin samples underwent cohesive failure [33]. Cohesive failure indicates excellent adhesion because the material will rather break than peel off or delaminate from the substrate. Brubaker and Messersmith [122] reviewed other DOPA-based and biologically inspired adhesive hydrogel systems developed earlier.

When developing tissue adhesives from hydrogels, both mechanical and adhesive properties will depend upon swelling

of the hydrogel. Swelling under physiological conditions usually results in weakening of the adhesive as well as decreased cohesive properties. Thus swelling will also reduce mechanical strength. To overcome this problem, Barrett et al. have developed a robust and negative-swelling adhesive hydrogel system that allows for controlling both mechanical strength and adhesion [123]. By using catechol-terminated block copolymers based on branched PPO–PEO (PPO=poly(propylene oxide), PEO=poly(ethylene oxide)), the authors synthesized hydrogels with adhesion values in the range of 50 kPa [123]. Through variation in polymer composition and by using the thermo-sensitive effect of PPO–PEO catechol-modified polymers, swelling could be reduced systematically.

Swelling can be a major problem when using adhesive tissue sealants. After application of the adhesive, swelling from surrounding fluid can, for example, restrict flow within a repaired blood vessel. Approaches to overcome this problem include new synthesis and formulation recipes as well as mixing procedures that improve already existing hydrogel adhesives. In one case, conjugation of DOPA to PEG-dextran aldehyde yields hydrogel adhesives that improve on PEG-dextran based sealants by performing well in wet conditions, even post swelling [32]. Burst pressure measurements were presented to evaluate how well such an adhesive hydrogel can repair puncture wounds. Compared to controls including PEG-dextran sealants [14], the modified PEG-dextran–DOPA swelled ~50 % less, had ~290 % greater stiffness and ~50 % greater adhesion [32].

Adhesive hydrogel-like coacervates can be made from polymers such as PEG-DA in the presence of a mixture of

copolyelectrolytes [124–126]. These copolyelectrolytes may contain, for example, 2-(methacryloyloxy) ethyl phosphate dopamine methacrylamide, poly(acrylamide-*co*-aminopropyl methacrylamide) and Ca^{2+} ions. Recent studies show that the resulting multiphase mixtures can reach maximum bond strengths of ca. 1.2 MPa [124]. The concept used for making these adhesives is based on mimicking the underwater glues of the sandcastle worm. Coacervates are not hydrogels, strictly speaking. These flowing precursor materials exist somewhere between a solid precipitate and a solution. Nonetheless the water content within the coacervate is high, hence the mention here. There are also parallels to double networks and ionically cross-linked hydrogels [124]. Applications for this adhesive are seen in the biomedical sector.

Other adhesive hydrogels based on interpenetrating networks

For tissue adhesives, hydrogels need to be designed with biocompatibility in mind. A PEG-dextran aldehyde-based adhesive with excess aldehyde groups may bring about enhanced adhesion strength. However, the presence of these functional groups will also induce inflammation *in vivo*. Artzi et al. [14] have attempted to balance adhesion strength with biological tolerance when fine-tuning adhesion for tissue specific applications. The hydrogel system of their choice was composed of aminated eight-arm star-PEG and dextran aldehyde. By controlling the number and density of active aldehyde groups, bonding could be balanced toward optimizing *in vivo* function. The active aldehyde groups are those remaining after the aminated star PEG and dextran aldehyde have reacted within the hydrogel network. These aldehydes can couple with amine groups from tissues thus enhancing adhesion. This cross-linking scheme is covalent and thus irreversible. Uniaxial loading of tissue adhesive samples provided maximum adhesion strengths around 0.57 N. Burst pressure measurements indicated strengths of ~130 kPa under triaxial loading conditions. The authors performed complementary atomic force microscopy experiments to evaluate the aldehyde density available for tissue cross-linking [14].

A similar class of PEG-based tissue adhesives can be made from chondroitin sulfate and polyethylene glycol. Strehin et al. [127] reported on a hydrogel adhesive synthesized from chondroitin sulfate that was functionalized with *N*-hydroxysuccinimide that can react with the primary amines of a six-arm PEG-amine. This system could covalently couple with amine groups from tissue for irreversible bonding. Adhesive strengths were modified by changing cohesive properties within the hydrogel. Adhesive performance of ca. 50 kPa is in a similar range to that of the DOPA based hydrogels. The highest storage modulus was ~37 kPa and burst pressure values were maximized at 80 mmHg.

Orthopedic tissue adhesion is proposed for this material [127, 128].

Other adhesive hydrogels are being synthesized and evaluated specifically for the repair of nerves. Among these adhesive systems, Amoozgar et al. [129] reported on semi-interpenetrating hydrogels from PEG and chitosan modified with 4-azidobenzoic acid. Hydrogel precursor solutions were photo cross-linked to nerve stumps to generate stiff and adhesive materials. The adhesion is based upon irreversible, covalent cross-linking directly to the tissue. Tensile analysis of nerve anastomosis (broken nerve stumps joined together by hydrogel glue) indicated maximum tolerated forces prior to failure of ~100 mN and maximum strains of ~20 %. These values are deemed to be in a range useful for nerve repair [129].

Adhesive nanocomposite hydrogels

Nanocomposite polymer hydrogels can be made to be both tough and elastomeric-like. However, these materials are usually not known to be adhesive. Gaharwar et al. [87] and Wu et al. [88] have discovered robust nanocomposite hydrogels with appreciable bonding properties, some of which are adhesive to moist surfaces as well as plastic, glass and skin. These hydrogels were made from a photopolymerized PEG-DA in the presence of silicate nanoparticles [87]. Adhesive strength values were around 13 kPa when 20 % of polymer and 5 % of silicate was used (the rest is water). The resulting hydrogel networks consist of (1) covalently cross-linked PEG-DA chains and (2) PEG chains that cross-link to Laponite with non-covalent bonding [40–42]. These non-covalent interactions, including ionic, dipole and hydrogen bonding, are likely responsible for the adhesion properties. Perhaps as a result of these interactions, bulk adhesion is reversible, thereby allowing removal of the material when no longer needed. Since this hydrogel system was discovered recently, the exact molecular interactions giving rise to adhesion still need to be determined.

Polyacrylic acid-based adhesive hydrogels

Additional interesting elastic and adhesive hydrogel systems have been reported including one by Arunbabu et al. [130]. Poly(acrylic acid-*co*-*N,N'*-methylenebisacrylamide) hydrogel films were made by copolymerizing acrylic acid with methylenebisacrylamide via photo polymerization [130]. The authors discuss how cross-link densities could be altered to balance elastic moduli and adhesive pull-off forces [130]. The highest elastic modulus for these materials was found around 0.6 MPa and adhesive pull off forces were around 3.2 mN. These polyacrylic acid-based hydrogel adhesives may be useful for tissue, mucosal and buccal adhesives [30] as well as sensing applications [130].

Conclusions and perspectives for the future

The experimental work reviewed here shows that tough and sticky hydrogels are gaining increased attention. These wet and tough materials are being explored for use in applications across a large technological spectrum (Figs. 2 and 3). Exciting possibilities are emerging in areas including cartilage repair, drug delivery, chemo-, bio-mechanical sensors, microfluidic devices with hydrogel operated valves, actuators, and even soft machines that are run by smart hydrogels. Additional ideas requiring soft and tough materials with controlled diffusion properties are now worth considering and evaluating [131].

Challenges that will be encountered mostly depend upon the design specifications of applications. For example, when stimuli responsive tough hydrogels are used in sensors and actuators, achieving long-term chemical and mechanical stability is an ongoing challenge. [132] Reproducibility of chemo-mechanical transduction, when chemical energy is converted into and from mechanical energy, remains difficult. When used in implants or for tissue engineering matrices, controlled degradation and nonfouling properties of hydrogels will be of critical relevance. Achieving a combination of several properties within one material is challenging. Perhaps even more difficult is making predictions about properties in advance of experiments [131]. Most tough hydrogels still cannot compete with the unique mechanical and structural properties of complex soft tissue. When hydrogels are considered for surgical adhesives, improved wet setting properties are desperately needed. So far, surgical adhesive can only aid, but not replace suturing.

The increasing number of publications in this area attests to the vibrancy of this research field. Original concepts to make tough hydrogels often begin with creative fundamental studies. Significant theoretical work has been published that aims to understand why and how hydrogels can be made tough. As for both tough and adhesive hydrogels there is little theory available. Once discovered, most tough and sticky hydrogels are then optimized and further evaluated with possible applications in mind. Nevertheless, whatever the motivation might be, tough hydrogels are still being intensively investigated. The yet unexplored potential of these tough and sticky materials offers many opportunities to be taken and new perspectives to be considered in the future.

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References

- Malmsten M (2011) Antimicrobial and antiviral hydrogels. *Soft Matter* 7:8725–8736
- Naficy S, Brown HR, Razal JM, Spinks GM, Whitten PG (2011) Progress toward robust polymer hydrogels. *Aust J Chem* 64:1007–1025
- Messing R, Schmidt AM (2011) Perspectives for the mechanical manipulation of hybrid hydrogels. *Polym Chem* 2:18–32
- Calvert P (2009) Hydrogels for soft machines. *Adv Mater* 21:743–756
- D. J. Beebe, J. S. Moore, J. M. Bauer, Q. Yu, R. H. Liu, C. Devadoss, and B. H. Jo, Functional hydrogel structures for autonomous flow control inside microfluidic channels, *Nature*, vol. 404, p. 588, Apr 6 2000.
- Dong XL, Wu RA, Dong J, Wu MH, Zhu Y, Zou HF (2009) Recent progress of polar stationary phases in CEC and capillary liquid chromatography. *Electrophoresis* 30:141–154
- Hempenius MA, Cirimi C, Lo Savio F, Song J, Vancso GJ (2010) Poly(ferrocenylsilane) gels and hydrogels with redox-controlled actuation. *Macromol Rapid Commun* 31:772–783
- G. Y. Huang, L. H. Zhou, Q. C. Zhang, Y. M. Chen, W. Sun, F. Xu, and T. J. Lu, Microfluidic hydrogels for tissue engineering, *Biofabrication*, vol. 3, Mar 2011.
- Allazetta S, Cosson S, Lutolf MP (2011) Programmable microfluidic patterning of protein gradients on hydrogels. *Chem Commun* 47:191–193
- Schneider HJ, Kato K, Strongin RM (2007) Chemomechanical polymers as sensors and actuators for biological and medicinal applications. *Sensors* 7:1578–1611
- Texter J (2009) Templating hydrogels. *Colloid Polym Sci* 287:313–321
- Kuckling D (2009) Responsive hydrogel layers—from synthesis to applications. *Colloid Polym Sci* 287:881–891
- Kim P, Zarzar LD, He XM, Grinthal A, Aizenberg J (2011) Hydrogel-actuated integrated responsive systems (HAIRS): moving towards adaptive materials. *Curr Opin Solid State Mater Sci* 15:236–245
- Artzi N, Zeiger A, Boehning F, Ramos AB, van Vliet K, Edelman ER (2011) Tuning adhesion failure strength for tissue-specific applications. *Acta Biomaterialia* 7:67–74
- Duarte AP, Coelho JF, Bordado JC, Cidade MT, Gil MH (2012) Surgical adhesives: systematic review of the main types and development forecast. *Prog Polym Sci* 37:1031–1050
- A. Matsumoto, R. Yoshida, and K. Kataoka, Glucose-responsive polymer gel bearing phenylborate derivative as a glucose-sensing moiety operating at the physiological pH, *Biomacromolecules*, vol. 5, pp. 1038–1045, May–Jun 2004.
- Thomas PC, Cipriano BH, Raghavan SR (2011) Nanoparticle-crosslinked hydrogels as a class of efficient materials for separation and ion exchange. *Soft Matter* 7:8192–8197
- Myung D, Farooqui N, Zheng LL, Koh W, Gupta S, Bakri A, Noolandi J, Cochran JR, Frank CW, Ta CN (2009) Bioactive interpenetrating polymer network hydrogels that support corneal epithelial wound healing. *J Biomed Mater Res Part A* 90A:70–81
- Huynh CT, Nguyen MK, Lee DS (2011) Injectable block copolymer hydrogels: achievements and future challenges for biomedical applications. *Macromolecules* 44:6629–6636
- Petrie EM (2007) Theories of adhesion. In: Patrie EM (ed) *Handbook of adhesives and sealants*. McGraw-Hill, New York
- Pizzi A, Mittal KL (1994) *Handbook of adhesive technology*. Marcel Dekker Inc., New York
- Pocius AV (2002) *Adhesion and adhesive technology*. An introduction. Carl Hanser Verlag, Munich
- Fitton MD, Broughton IG (2005) Variable modulus adhesives: an approach to optimised joint performance. *Int J Adhes Adhes* 25:329–336
- Davies ML, Murphy SM, Hamilton CJ, Tighe BJ (1992) Polymer membranes in clinical sensor applications: 3. Hydrogels as reactive matrix membranes in fiber optic sensors. *Biomaterials* 13:991–999

25. Petersen S, Gattermayer M, Biesalski M (2011) Hold on at the right spot: bioactive surfaces for the design of live-cell micropatterns. *Bioactive Surfaces* 240:35–78
26. Lin CC, Anseth KS (2009) PEG hydrogels for the controlled release of biomolecules in regenerative medicine. *Pharm Res* 26:631–643
27. Park K, Shalaby SWS, Park H (1993) *Biodegradable Hydrogels for Drug Delivery*. Technomic Publishing, Lancaster, PA
28. S. Chaterji, I. K. Kwon, and K. Park, Smart polymeric gels: redefining the limits of biomedical devices, *Progress in Polymer Science*, vol. 32, pp. 1083–1122, Aug–Sep 2007.
29. Bird SP, Baker LA (2011) Biologically modified hydrogels for chemical and biochemical analysis. *Analyst* 136:3410–3418
30. Bait N, Grassl B, Deraill C, Benaboura A (2011) Hydrogel nanocomposites as pressure-sensitive adhesives for skin-contact applications. *Soft Matter* 7:2025–2032
31. Peng HT, Shek PN (2010) Novel wound sealants: biomaterials and applications. *Expert Rev Med Devices* 7:639–659
32. Shazly TM, Baker AB, Naber JR, Bon A, Van Vliet KJ, Edelman ER (2010) Augmentation of postswelling surgical sealant potential of adhesive hydrogels. *J Biomed Mater Res Part A* 95A:1159–1169
33. Brubaker CE, Messersmith PB (2011) Enzymatically degradable mussel-inspired adhesive hydrogel. *Biomacromolecules* 12:4326–4334
34. Dolgin E (2013) The sticking point. *Nat Med* 19:124–125
35. Haque MA, Kurokawa T, Gong JP (2012) Super tough double network hydrogels and their application as biomaterials. *Polymer* 53:1805–1822
36. Okumura Y, Ito K (2001) The polyrotaxane gel: a topological gel by figure-of-eight cross-links. *Adv Mater* 13:485–487
37. Sakai T, Matsunaga T, Yamamoto Y, Ito C, Yoshida R, Suzuki S, Sasaki N, Shibayama M, Chung UI (2008) Design and fabrication of a high-strength hydrogel with ideally homogeneous network structure from tetrahedron-like macromonomers. *Macromolecules* 41:5379–5384
38. Henderson KJ, Zhou TC, Otim KJ, Shull KR (2010) Ionically cross-linked triblock copolymer hydrogels with high strength. *Macromolecules* 43:6193–6201
39. K. Haraguchi and T. Takehisa, Nanocomposite hydrogels: a unique organic–inorganic network structure with extraordinary mechanical, optical, and swelling/de-swelling properties, *Advanced Materials*, vol. 14, pp. 1120–1124, AUG 16 2002.
40. Schexnaider PJ, Schmidt G (2009) Nanocomposite polymer hydrogels. *Colloid Polym Sci* 287:1–11
41. Shibayama M (2012) Structure–mechanical property relationship of tough hydrogels. *Soft Matter* 8:8030–8038
42. Schexnaider P, Loizou E, Porcar L, Butler P, Schmidt G (2009) Heterogeneity in nanocomposite hydrogels from poly(ethylene oxide) cross-linked with silicate nanoparticles. *Phys Chem Chem Phys* 11:2760–2766
43. Myung D, Waters D, Wiseman M, Duhamel PE, Noolandi J, Ta CN, Frank CW (2008) Progress in the development of interpenetrating polymer network hydrogels. *Polym Adv Technol* 19:647–657
44. Kopecek J (2009) Hydrogels: from soft contact lenses and implants to self-assembled nanomaterials. *J Polym Sci Part A-Polym Chem* 47:5929–5946
45. Fisher OZ, Khademhosseini A, Langer R, Peppas NA (2010) Bioinspired materials for controlling stem cell fate. *Acc Chem Res* 43:419–428
46. Buenger D, Topuz F, Groll J (2012) Hydrogels in sensing applications. *Prog Polym Sci* 37:1678–1719
47. Van Vlierberghe S, Dubruel P, Schacht E (2011) Biopolymer-based hydrogels as scaffolds for tissue engineering applications: a review. *Biomacromolecules* 12:1387–1408
48. Dvir T, Timko BP, Kohane DS, Langer R (2011) Nanotechnological strategies for engineering complex tissues. *Nat Nanotechnol* 6:13–22
49. J. Patterson, M. M. Martino, and J. A. Hubbell, Biomimetic materials in tissue engineering, *Materials Today*, vol. 13, pp. 14–22, Jan–Feb 2010.
50. Stevens MM, Khademhosseini A (2010) Emerging materials for tissue engineering and regenerative medicine: themed issue for *Soft Matter* and *Journal of Materials Chemistry*. *Soft Matter* 6:4962–4962
51. Kloxin AM, Lewis KJR, DeForest CA, Seedorf G, Tibbitt MW, Balasubramaniam V, Anseth KS (2012) Responsive culture platform to examine the influence of microenvironmental geometry on cell function in 3D. *Integr Biol* 4:1540–1549
52. Gong JP, Katsuyama Y, Kurokawa T, Osada Y (2003) Double-network hydrogels with extremely high mechanical strength. *Adv Mater* 15:1155–1158
53. Gong JP (2010) Why are double network hydrogels so tough? *Soft Matter* 6:2583–2590
54. Brown HR (2007) A model of the fracture of double network gels. *Macromolecules* 40:3815–3818
55. Webber RE, Creton C, Brown HR, Gong JP (2007) Large strain hysteresis and mullins effect of tough double-network hydrogels. *Macromolecules* 40:2919–2927
56. Y. Tanaka, A local damage model for anomalous high toughness of double-network gels, *Epl*, vol. 78, 2007.
57. L. Mullins and N. R. Tobin, Stress softening in rubber vulcanizates: I. Use of a strain amplification factor to describe elastic behavior of filler-reinforced vulcanized rubber, *Journal of Applied Polymer Science*, vol. 9, pp. 2993–, 1965.
58. Ito K (2012) Novel entropic elasticity of polymeric materials: why is slide-ring gel so soft? *Polym J* 44:38–41
59. Tirumala VR, Tominaga T, Lee S, Butler PD, Lin EK, Gong JP, Wu WL (2008) Molecular model for toughening in double-network hydrogels. *J Phys Chem B* 112:8024–8031
60. Baumberger T, Caroli C, Martina D (2006) Solvent control of crack dynamics in a reversible hydrogel. *Nat Mater* 5:552–555
61. Okumura K (2004) Toughness of double elastic networks. *Europhys Lett* 67:470–476
62. Kishi R, Hiroki K, Tominaga T, Sano KI, Okuzaki H, Martinez JG, Otero TF, Osada Y (2012) Electro-conductive double-network hydrogels. *J Polymer Sci, Part B: Polymer Phys* 50:790–796
63. Cui J, Lackey MA, Madkour AE, Saffer EM, Griffin DM, Bhatia SR, Crosby AJ, Tew GN (2012) Synthetically simple, highly resilient hydrogels. *Biomacromolecules* 13:584–588
64. Cui J, Lackey MA, Tew GN, Crosby AJ (2012) Mechanical properties of end-linked PEG/PDMS hydrogels. *Macromolecules* 45:6104–6110
65. Zhang XY, Guo XL, Yang SG, Tan SX, Li XF, Dai HJ, Yu XL, Zhang XL, Weng N, Jian B, Xu J (2009) Double-network hydrogel with high mechanical strength prepared from two biocompatible polymers. *J Appl Polym Sci* 112:3063–3070
66. Harrass K, Kruger R, Moller M, Albrecht K, Groll J (2013) Mechanically strong hydrogels with reversible behaviour under cyclic compression with MPa loading. *Soft Matter* 9:2869–2877
67. Rakovsky A, Marbach D, Lotan N, Lanir Y (2009) Poly(ethylene glycol)-based hydrogels as cartilage substitutes: synthesis and mechanical characteristics. *J Appl Polym Sci* 112:390–401
68. Brigham MD, Bick A, Lo E, Bendali A, Burdick JA, Khademhosseini A (2009) Mechanically robust and bioadhesive collagen and photocrosslinkable hyaluronic acid semi-interpenetrating networks. *Tissue Eng Part A* 15:1645–1653
69. Liu YX, Chan-Park MB (2009) Hydrogel based on interpenetrating polymer networks of dextran and gelatin for vascular tissue engineering. *Biomaterials* 30:196–207

70. DeKosky BJ, Dormer NH, Ingavle GC, Roatch CH, Lomakin J, Detamore MS, Gehrke SH (2010) Hierarchically designed agarose and poly(ethylene glycol) interpenetrating network hydrogels for cartilage tissue engineering. *Tissue Eng Part C-Methods* 16:1533–1542
71. Chan BK, Wippich CC, Wu CJ, Sivasankar PM, Schmidt G (2012) Robust and semi-interpenetrating hydrogels from poly(ethylene glycol) and collagen for elastomeric tissue scaffolds. *Macromol Biosci* 12:1490–1501
72. Wang XZ, Wang HL, Brown HR (2011) Jellyfish gel and its hybrid hydrogels with high mechanical strength. *Soft Matter* 7:211–219
73. Shull KR (2012) Materials science: a hard concept in soft matter. *Nature* 489:36–37
74. Sun JY, Zhao XH, Illeperuma WRK, Chaudhuri O, Oh KH, Mooney DJ, Vlassak JJ, Suo ZG (2012) Highly stretchable and tough hydrogels. *Nature* 489:133–136
75. Tuncaboylu DC, Sari M, Oppermann W, Okay O (2011) Tough and self-healing hydrogels formed via hydrophobic interactions. *Macromolecules* 44:4997–5005
76. P. Manandhar, P. D. Calvert, and J. R. Buck, Elastomeric ionic hydrogel sensor for large strains, *IEEE Sensors Journal*, vol. 12, Jun 2012.
77. Wang Q, Mynar JL, Yoshida M, Lee E, Lee M, Okuro K, Kinbara K, Aida T (2010) High-water-content mouldable hydrogels by mixing clay and a dendritic molecular binder. *Nature* 463:339–343
78. Lin HR, Ling MH, Lin YJ (2009) High strength and low friction of a PAA–alginate–silica hydrogel as potential material for artificial soft tissues. *J Biomater Sci Polym Ed* 20:637–652
79. D. W. Thompson and J. T. Butterworth, The nature of laponite and its aqueous dispersions, *Journal of Colloid and Interface Science*, vol. 151, pp. 236–243, JUN 1992.
80. H. Tanaka, S. Jabbari-Farouji, J. Meunier, and D. Bonn, Kinetics of ergodic-to-nonergodic transitions in charged colloidal suspensions: Aging and gelation, *Physical Review E*, vol. 71, Feb 2005.
81. H. Tanaka, J. Meunier, and D. Bonn, Nonergodic states of charged colloidal suspensions: repulsive and attractive glasses and gels, *Physical Review E*, vol. 69, Mar 2004.
82. Haraguchi K (2011) Synthesis and properties of soft nanocomposite materials with novel organic/inorganic network structures. *Polym J* 43:223–241
83. T. Nishida, H. Endo, N. Osaka, H. Li, K. Haraguchi, and M. Shibayama, Deformation mechanism of nanocomposite gels studied by contrast variation small-angle neutron scattering, *Physical Review E*, vol. 80, Sep 2009.
84. Ren HY, Zhu MF, Haraguchi K (2012) Effects of counter ions of clay platelets on the swelling behavior of nanocomposite gels. *J Colloid Interface Sci* 375:134–141
85. H. Furukawa, K. Horie, R. Nozaki, and M. Okada, Swelling-induced modulation of static and dynamic fluctuations in polyacrylamide gels observed by scanning microscopic light scattering, *Physical Review E*, vol. 68, Sep 2003.
86. Wu CJ, Gaharwar AK, Chan BK, Schmidt G (2011) Mechanically tough pluronic F127/Laponite nanocomposite hydrogels from covalently and physically cross-linked Networks. *Macromolecules* 44:8215–8224
87. Gaharwar AK, Rivera CP, Wu CJ, Schmidt G (2011) Transparent, elastomeric and tough hydrogels from poly(ethylene glycol) and silicate nanoparticles. *Acta Biomater* 7:4139–4148
88. Wu C-J, Wilker JJ, Schmidt G (2013) Robust and adhesive hydrogels from cross-linked poly(ethylene glycol) and silicate for biomedical use. *Macromol Biosci* 13:59–66
89. Gaharwar AK, Dammu SA, Canter JM, Wu CJ, Schmidt G (2011) Highly Extensible, tough, and elastomeric nanocomposite hydrogels from poly(ethylene glycol) and hydroxyapatite nanoparticles. *Biomacromolecules* 12:1641–1650
90. Lin WC, Marcellan A, Hourdet D, Creton C (2011) Effect of polymer–particle interaction on the fracture toughness of silica filled hydrogels. *Soft Matter* 7:6578–6582
91. G. J. Lake and A. G. Thomas, Strength of highly elastic materials, *Proceedings of the Royal Society of London Series a-Mathematical and Physical Sciences*, vol. 300, pp. 108–, 1967.
92. Wang Q, Hou RX, Cheng YJ, Fu J (2012) Super-tough double-network hydrogels reinforced by covalently compositing with silica-nanoparticles. *Soft Matter* 8:6048–6056
93. Liu JQ, Chen CF, He CC, Zhao L, Yang XJ, Wang HL (2012) Synthesis of graphene peroxide and its application in fabricating super extensible and highly resilient nanocomposite hydrogels. *ACS Nano* 6:8194–8202
94. Qin XP, Zhao F, Liu YK, Wang HY, Feng SY (2009) High mechanical strength hydrogels preparation using hydrophilic reactive microgels as crosslinking agents. *Colloid Polym Sci* 287:621–625
95. T. Huang, H. G. Xu, K. X. Jiao, L. P. Zhu, H. R. Brown, and H. L. Wang, A novel hydrogel with high mechanical strength: A macromolecular microsphere composite hydrogel, *Advanced Materials*, vol. 19, pp. 1622–, Jun 18 2007.
96. Xia LW, Ju XJ, Liu JJ, Xie R, Chu LY (2010) Responsive hydrogels with poly(*N*-isopropylacrylamide-*co*-acrylic acid) colloidal spheres as building blocks. *J Colloid Interface Sci* 349:106–113
97. Xu K, Tan Y, Chen Q, An HY, Li WB, Dong LS, Wang PX (2010) A novel multi-responsive polyampholyte composite hydrogel with excellent mechanical strength and rapid shrinking rate. *J Colloid Interface Sci* 345:360–368
98. Hu J, Kurokawa T, Hiwatashi K, Nakajima T, Wu ZL, Liang SM, Gong JP (2012) Structure optimization and mechanical model for microgel-reinforced hydrogels with high strength and toughness. *Macromolecules* 45:5218–5228
99. Meid J, Dierkes F, Cui J, Messing R, Crosby AJ, Schmidt A, Richtering W (2012) Mechanical properties of temperature sensitive microgel/polyacrylamide composite hydrogels—from soft to hard fillers. *Soft Matter* 8:4254–4263
100. Meid J, Friedrich T, Tieke B, Lindner P, Richtering W (2011) Composite hydrogels with temperature sensitive heterogeneities: influence of gel matrix on the volume phase transition of embedded poly(*N*-isopropylacrylamide) microgels. *Phys Chem Chem Phys* 13:3039–3047
101. Lehmann S, Seiffert S, Richtering W (2012) Spatially resolved tracer diffusion in complex responsive hydrogels. *J Am Chem Soc* 134:15963–15969
102. Harada A, Hashidzume A, Yamaguchi H, Takashima Y (2009) Polymeric rotaxanes. *Chem Rev* 109:5974–6023
103. Kato K, Komatsu H, Ito K (2010) A versatile synthesis of diverse polyrotaxanes with a dual role of cyclodextrin as both the cyclic and capping components. *Macromolecules* 43:8799–8804
104. Kato K, Inoue K, Kidowaki M, Ito K (2009) Organic–inorganic hybrid slide-ring gels: polyrotaxanes consisting of poly(dimethylsiloxane) and gamma-cyclodextrin and subsequent topological cross-linking. *Macromolecules* 42:7129–7136
105. Matsunaga T, Sakai T, Akagi Y, Chung U, Shibayama M (2009) Structure Characterization of tetra-PEG gel by small-angle neutron scattering. *Macromolecules* 42:1344–1351
106. Akagi Y, Matsunaga T, Shibayama M, Chung U, Sakai T (2010) Evaluation of topological defects in tetra-PEG gels. *Macromolecules* 43:488–493
107. Matsunaga T, Sakai T, Akagi Y, Chung UI, Shibayama M (2009) SANS and SLS Studies on tetra-arm PEG Gels in as-prepared and swollen states. *Macromolecules* 42:6245–6252
108. Abdurrahmanoglu S, Can V, Okay O (2009) Design of high-toughness polyacrylamide hydrogels by hydrophobic modification. *Polymer* 50:5449–5455

109. Friedrich T, Tieke B, Stadler FJ, Bailly C (2011) Improvement of elasticity and strength of poly(*N*-isopropylacrylamide) hydrogels upon copolymerization with cationic surfimers. *Soft Matter* 7:6590–6597
110. Thomas JD, Fussell G, Sarkar S, Lowman AM, Marcolongo M (2010) Synthesis and recovery characteristics of branched and grafted PNIPAAm-PEG hydrogels for the development of an injectable load-bearing nucleus pulposus replacement. *Acta Biomater* 6:1319–1328
111. Wang M, Kornfield JA (2012) Measuring shear strength of soft-tissue adhesives. *J Biomed Mater Res Part B-Appl Biomater* 100B:618–623
112. Mintzer MA, Grinstaff MW (2011) Biomedical applications of dendrimers: a tutorial. *Chem Soc Rev* 40:173–190
113. Oelker AM, Berlin JA, Wathier M, Grinstaff MW (2011) Synthesis and characterization of dendron cross-linked PEG Hydrogels as corneal adhesives. *Biomacromolecules* 12:1658–1665
114. M. Wathier and M. W. Grinstaff, Hydrogel sealants for wound repair in ophthalmic surgery, *Biomaterials and Regenerative Medicine in Ophthalmology*, pp. 411–432, 2009.
115. Sedo J, Saiz-Poseu J, Busque F, Ruiz-Molina D (2013) Catechol-based biomimetic functional materials. *Adv Mater* 25:653–701
116. Wilker JJ (2010) Marine bioinorganic materials: mussels pumping iron. *Curr Opin Chem Biol* 14:276–283
117. Wilker JJ (2010) The iron-fortified adhesive system of marine mussels. *Angew Chem Int Ed* 49:8076–8078
118. Wilker JJ (2011) Biomaterials: Redox and adhesion on the rocks. *Nat Chem Biol* 7:579–580
119. Mehdizadeh M, Weng H, Gyawali D, Tang LP, Yang J (2012) Injectable citrate-based mussel-inspired tissue bioadhesives with high wet strength for sutureless wound closure. *Biomaterials* 33:7972–7983
120. Brubaker CE, Kissler H, Wang LJ, Kaufman DB, Messersmith PB (2010) Biological performance of mussel-inspired adhesive in extrahepatic islet transplantation. *Biomaterials* 31:420–427
121. Haller CM, Buerzle W, Brubaker CE, Messersmith PB, Mazza E, Ochsenein-Koelble N, Zimmermann R, Ehrbar M (2011) Mussel-mimetic tissue adhesive for fetal membrane repair: a standardized ex vivo evaluation using elastomeric membranes. *Prenat Diagn* 31:654–660
122. Brubaker CE, Messersmith PB (2012) The present and future of biologically inspired adhesive interfaces and materials. *Langmuir* 28:2200–2205
123. D. J. Barrett, G. G. Bushnell, and P. B. Messersmith, Mechanically robust, negative-swelling, mussel-inspired tissue adhesive, *Advanced Healthcare Materials*, vol. DOI: 10.1001/adhm.201200316, 2012.
124. Kaur S, Weerasekare GM, Stewart RJ (2011) Multiphase Adhesive coacervates inspired by the sandcastle worm. *ACS Appl Mater Interfaces* 3:941–944
125. H. Shao and R. J. Stewart, Biomimetic underwater adhesives with environmentally triggered setting mechanisms, *Advanced Materials*, vol. 22, pp. 729–+, Feb 9 2010.
126. Shao H, Bachus KN, Stewart RJ (2009) A water-borne adhesive modeled after the sandcastle glue of *P-californica*. *Macromol Biosci* 9:464–471
127. Strehin I, Nahas Z, Arora K, Nguyen T, Elisseeff J (2010) A versatile pH sensitive chondroitin sulfate-PEG tissue adhesive and hydrogel. *Biomaterials* 31:2788–2797
128. Simson J, Crist J, Strehin I, Lu QZ, Elisseeff JH (2013) An orthopedic tissue adhesive for targeted delivery of intraoperative biologics. *J Orthop Res* 31:392–400
129. Amoozgar Z, Rickett T, Park J, Tucek C, Shi RY, Yeo Y (2012) Semi-interpenetrating network of polyethylene glycol and photocrosslinkable chitosan as an in-situ-forming nerve adhesive. *Acta Biomater* 8:1849–1858
130. Arunbabu D, Shahsavan H, Zhang W, Zhao BX (2013) Poly(AA-co-MBA) hydrogel films: adhesive and mechanical properties in aqueous medium. *J Phys Chem B* 117:441–449
131. Iyer BVS, Salib IG, Yashin VV, Kowalewski T, Matyjaszewski K, Balazs AC (2013) Modeling the response of dual cross-linked nanoparticle networks to mechanical deformation. *Soft Matter* 9:109–121
132. Calvo-Marzal P, Delaney MP, Auletta, JT, Pan T, Perri NM, Weiland LM, Waldeck DH, Clark WW, Meyer TY (2012) Manipulating mechanical properties with electricity: Electroplastic elastomer hydrogels. *ACS Macro Letters* 1:204–208