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Stimuli-Responsive Toughening of Hydrogels

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14 ABSTRACT

15 Materials with stimuli-switchable properties are widespread in nature. Through
16 biomimicry, stimuli-responsive hydrogels have received increasing research in recent
17 years. In particular, hydrogels with stimuli-tunable mechanical properties provide an
18 important platform for designing new materials with specific applications such as 3D
19 printing, soft robot, and tunable adhesion. Herein, the state-of-the-art of hydrogels with
20 stimuli-responsive toughness is reviewed in detail. Characteristic reinforcement
21 mechanisms are fully discussed first, followed by systematical demonstrations of various
22 smart hydrogels responding to various stimuli. In particular, special attention is paid to
23 thermal, light, pH, and salt triggers because of their broad applications and easy
24 implementation. Furthermore, the applications of these smart hydrogels are included. In
25 addition to the overview of recent advances, we finally summarize the critical challenges
26 of current discoveries and make an outlook for the following work, which we anticipate to
27 lead to substantial progress of these responsive materials in the future.

28

Introduction

Living materials consist of various smart components whose performance can be finely tuned by stimuli. For instance, muscles reversibly stiffen or soften in response to neutral signals, chameleons hold the ability to change color in response to several environmental triggers, and *Mimosa Pudica* leaves close automatically under mechanical disturbances. Learning from nature, bio-inspired materials with stimuli-responsiveness have attracted considerable attention during the last few decades.¹ In particular, stimuli-responsive hydrogels, which are often termed as smart hydrogels, have been intensively investigated as they automatically respond to environmental changes.²⁻³ Bearing high level of water contents, hydrogels serve as ideal candidates for bio-engineering applications as they share versatile similarities with human tissues.⁴⁻⁵ Moreover, their ability to be programmed concerning one or various given stimuli considerably broadens their application perspectives. Typical stimuli involve temperature, pH, humidity, light, specific ions or molecules, electrical field, magnetic field, solvent, and ionic strength. Therefore, these smart hydrogels demonstrate great potential for developing specific applications, from targeted drug delivery⁶ to precisely controlled actuators,⁷⁻⁸ from artificial muscles⁹ to self-healable tissue,¹⁰ and from photochromic windows¹¹ to magnetic sensors.¹²

When subjected to external stimuli, the response of hydrogels is transmitted from the microscopic level to the macroscopic scale. Their optical transparency is easily tunable, their size and shape are readily controllable, and their hydrophilicity is finely adjustable.¹³

49 Apart from these features, smart hydrogels can also demonstrate switchable mechanical
50 performance, with dramatic modifications of their rigidity, extensibility, and toughness.
51 Therefore, these hydrogels are able to adapt to complex environments and can be used in
52 relevant applications where stimuli-tunable soft materials are required. For example, a soft
53 robot needs the mechanical responsiveness of its components in order to accomplish a
54 complex movement.¹⁴

55 While stimuli-responsive hydrogels have already been adequately addressed and fully
56 summarized based on their tunable size,¹⁵ color,¹⁶ and even electro-conductivity,² the
57 control of their mechanical properties by environmental stimuli has been much less
58 investigated and rationalized. To fill this gap, recent advances in the field of three-
59 dimensional hydrogels with stimuli-responsive toughness are highlighted and summarized
60 in this review (Figure 1). Associating polymer solutions that undergo sol-gel transition and
61 form transient unstable weak networks are excluded from the discussion. In the first part,
62 the different mechanisms involved in the viscoelastic response of hydrogels are carefully
63 discussed before describing the main stimuli used to modify their mechanical performances.
64 Special attention is given to thermal, light, pH, and salt responsive hydrogels. The
65 responsive mechanical properties of hydrogels are explored and both the advantages and
66 weaknesses of these smart systems are discussed. Finally, this review provides concluding
67 remarks over the recent advances and challenges in this field with some guiding ideas
68 which could inspired new findings.

Figure 1. Schematic illustration of hydrogels with stimuli-responsive mechanical performance.

1. Mechanisms of hydrogels with responsive mechanical performance

Before discussing the stimuli-responsiveness, it is important to briefly recall some basic elements relating to the viscoelastic properties of hydrogels, typically the elastic and dissipative behaviors. Hydrogels are soft materials composed of crosslinked polymer chains typically swollen with water. While absorbing a large amount of solvent inside the three-dimensional network with osmotic pressure contribution, hydrogels still maintain solid-state with certain levels of mechanical performance. The swelling and elasticity of hydrogels are directly related to the crosslink density of the network, its polymer volume fraction as well as the interactions between solvent and polymer. According to the classical

theory of rubber elasticity,¹⁷⁻¹⁸ the shear modulus G of swollen hydrogel having no permanent (trapped) entanglements can be described by the relation below,

$$G \cong kTv_{e,\phi} = \frac{RT\rho_0\phi_0^a\phi^b}{M_0N} \quad (1)$$

with $v_{e,\phi}$ the number density of elastically active chains at the polymer volume fraction ϕ , k the Boltzmann constant, R the gas constant, T the temperature, ϕ_0 the polymer volume fraction in the preparation state, ρ_0 the polymer density, M_0 the molar mass of the monomer, and N the number of monomers per elastic strand. In equation (1), a and b are scaling exponents which depend on the quality of the solvent ($a = 2/3$, $b = 1/3$ in θ conditions and $a = 5/12$, $b = 7/12$ in a good solvent), with $G \sim \phi_0$ for gels in the preparation state ($\phi = \phi_0$). From equation (1), we can see that the polymer volume fraction, the quality of solvent, and the molar mass between crosslinks determine the elastic modulus for a given hydrogel. This concentration dependence is valid for chemical networks having no permanent (trapped) entanglements which means that N is shorter than the length of an entanglement strand at the preparation concentration $N_e(\phi_0)$. In the opposite situation, $N_e(\phi_0) < N$, the elastic properties are dominated by entanglements and $G \sim RT\phi_0^c\phi^d$ ($c = 2$, $d = 1/3$ in θ conditions and $c = 5/3$, $d = 7/12$ in a good solvent); with $G \sim \phi_0^{2.3}$ for gels in the preparation state.¹⁸ All these equations derived from linear elasticity, assuming Gaussian statistics for polymer chains, hold at low deformation. This is no longer the case when the chains are subjected to larger deformations where more sophisticated statistical approaches may be

used, like Langevin statistics¹⁹ to model the nonlinear rubber elasticity. This is the case for highly swollen polyelectrolyte networks which become stiffer (G increases) when the chains are stretched with the swelling ($v_{e,\phi}$ decreases).²⁰

While the stiffness of swollen polymer networks is something relatively well understood and quite easily controlled, hydrogels remain fragile materials. Indeed, they are characterized by low mechanical properties in terms of extensibility and tenacity which are currently a hot topic in the scientific community of hydrogels. Experimentally, the measured strain and stress at break of material correspond to the point where a crack propagates through the sample. Therefore, we can assume, as proposed by Maugis and Barquins,²¹ that the interfacial fracture energy $\Gamma(v)$ can be empirically written as:

$$\Gamma(v) = \Gamma_0(1 + f(a_T v)) \quad (2)$$

where $f(a_T v)$ is a velocity-dependent dissipative factor with v the crack velocity and a_T the time-temperature superposition shift factor; Γ_0 is the threshold fracture energy for vanishing crack velocities, mostly related to the chemistry of the interface. Based on the molecular theory for Γ_0 developed by Lake *et al.*,²² when any of the main chain bonds break, the total bond energy of each bond of the stretched chain is irreversibly lost. Therefore, the minimum energy necessary to break the chain is proportional to the length of that chain, *i.e.*, to the number of C-C bonds comprising that N -chain. Assuming that only the strands crossing the fracture plane will break for a homogeneously crosslinked hydrogel, Γ_0 can be

written as:²²⁻²³

$$\Gamma_0 = NU_b\Sigma \approx U_b v_{e,\phi=1} \phi a N^{\frac{3}{2}} \approx \frac{U_b a \rho_0 \phi}{M_0} N^{\frac{1}{2}} \quad (3)$$

where Σ is the areal density of strands crossing the interface, U_b is the bond energy of a C-C bond (~ 350 kJ/mol), $v_{e,\phi=1}$ the number density of elastically active chains in the melt state and a is the size of the monomer. From this equation, it turns out that the fracture energy of hydrogels is also related to their polymer volume fraction and crosslinking density, though the dependence is distinct from that on elastic shear modulus. Indeed, the crosslinking density, which is directly related to reciprocal N , is positively related to G but negatively contributes to Γ . Consequently, there is a trade-off between rigidity and toughness. In contrast, both G and Γ demonstrate a consistent relationship to ϕ , which means that both rigidity and toughness decrease when the gel swells; i.e. ϕ decreases.

Based on equation (2), the velocity-dependent dissipative factor $f(a_T v)$ also plays an important role in determining hydrogels' toughness. This factor, which considers the mechanical dissipation in the bulk, is related to the crack velocity v and the time-temperature superposition shift factor a_T . Along with the crack propagation velocity, the rise of molecular friction and noncovalent interactions between polymer chains increase dissipation processes and these effects have been clearly shown to significantly increase the fracture energy of soft materials.²⁴⁻²⁵ For water-swollen hydrogels, which are generally characterized by a low polymer volume fraction and a weak dissipative factor, physical

interactions²⁶⁻²⁷ that can reversibly break under stretch can significantly enhance the hydrogels toughness. Moreover, the plasticity of the gel, which can be implemented by incorporating stiffer domains that can only be deformed above a certain stress level, can also greatly contribute to the hydrogel strengthening.²⁸⁻²⁹

Considering the above theories, the mechanical performances of hydrogels strongly depend on the crosslink density, the volume fraction, and the polymer chain interactions. By tuning these factors with external triggers, stimuli-responsive hydrogels can toughen or soften on demand. As shown in Figure 2, the typical mechanisms involve noncovalent interactions, formation or scission of covalent bonds, change in water content, phase separation, etc.

Figure 2. Mechanisms of hydrogels with responsive toughness. a) Noncovalent interactions. b) Formation or scission of covalent bonds. c) Volume change. d) Phase separation. Reproduced with permission.³⁰ Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA.

1.1 Influence of noncovalent interactions

Generally, stimuli-responsive hydrogels develop various noncovalent interactions within their three-dimensional polymer networks.^{24, 31} These noncovalent interactions includes hydrophobic interactions,³² hydrogen-bonds,³³ dipole-dipole interactions,³⁴ coordinate bonds,³⁵ etc. These interactions may serve as dynamic bonds under stretch, thus increasing the dissipative factor and then toughening the hydrogels. When subjected to environmental signals, the strength of these physical interactions can be reversibly/irreversibly influenced. For example, hydrogen bonds are generally temperature-dependent,³⁶ the strength of coordinate bonds is often sensitive to environmental pH conditions³⁷⁻³⁸ and the association between anions and cations is likely to be screened by the addition of salts.³⁹ Therefore, the application of environmental stimuli can easily lead to responsive stiffening or weakening of hydrogels.

1.2 Formation or scission of covalent bonds

When experiencing environmental variations, new covalent bonds may form or/and existing covalent bonds may break. Along with the formation or scission of covalent bonds, the effective crosslinking degree of hydrogels is affected and consequently its mechanical properties. This is somewhat more ubiquitous in light-responsive hydrogels, as the high energy of light is able to readily influence chemical bonds, including the cleavage,⁴⁰ addition,⁴¹ exchange,⁴²⁻⁴³ and isomerization.⁴⁴⁻⁴⁵ The shape and toughness of light-sensitive

hydrogels can be modulated by adjusting wavelength or time of irradiation.⁴¹

1.3 Volume change

Both elastic and fracture behavior of hydrogel are highly affected by its water content. According to the theories of rubber elasticity and Lake-Thomas⁴⁶ discussed previously, both rigidity (G) and toughness (I) of hydrogels increase with the polymer volume fraction (ϕ) and then decrease with the swelling of the gel ($Q = 1/\phi = V_{sw}/V_{dry}$), with Q the swelling ratio and V_{sw} , V_{dry} the swollen and dry volumes of the gel. External stimuli may then induce a variation of the osmotic pressure within the polymer network, giving rise to water diffusion inside or outside the gel which will consequently affect its mechanical properties. At the same time, large volume contractions can also induce stronger polymer interactions⁴⁷ thus leading to further reinforcement of the hydrogels.

1.4 Phase separation

Upon stimuli changing the environmental conditions, water may shift from a good solvent to a poor solvent for the polymer network. In such a case, the gels tend to become opaque due to phase separation giving rise to an alternation of dense and sparse polymer regions forming discontinuous or bicontinuous domains at the submicron scale.⁴⁸⁻⁴⁹ While the rich polymer phase forms a load-bearing scaffold percolating through the whole network in response to the stimulus, the mechanical performances of the gel are simultaneously

modulated. For instance, Shibayama et al. have detailed the change of viscoelastic properties of thermo-responsive hydrogels upon phase separation.⁵⁰ Compared to other aforementioned mechanisms, the phase separation process has a much greater impact on the reinforcement of hydrogels. When a hydrophilic polyacrylamide hydrogel is transferred from water to a *N,N*-dimethylformamide (DMF)/water mixture, the gel undergoes rapid phase separation and demonstrates a strong improvement in stiffness, toughness, with self-healing properties and an increased elastic modulus over more than 4 decades.⁵¹ A similar behavior was reported with the phase separation of *N,N*-dimethylacrylamide hydrogel induced by inorganic additives with an abrupt change of mechanical properties around the transition point.⁵²

It is worthwhile mentioning that more than one mechanism may play a synergistic effect in the responsive regulation of the mechanical performances of smart hydrogels. Taking for instance thermo-responsive poly(*N*-isopropylacrylamide) hydrogel, the material is remarkably strengthened when heated above the phase transition temperature with the synergistic contribution of enhanced physical interactions, shrinkage, and phase separation.⁵³ Although the above mechanisms generally go hand in hand, it is important to stress that the phase separation phenomenon largely dominates the others. It can even lead to a mechanical reinforcement of the gel even when the latter swells during the phase separation, as recently shown in the case of organogels immersed in water.⁵⁴

Various physical or chemical stimuli may induce toughening or weakening of hydrogels according to the mechanisms discussed above. Within the field of responsive hydrogels, thermal, light, pH, and salt stimuli were mostly investigated in the past few years although other triggers, such as magnetic⁵⁵ or electric fields,⁵⁶⁻⁵⁸ can also be used to stimulate the mechanical properties. In the following, we will review relevant examples of smart hydrogels whose mechanical properties can be switched by different signals and discuss their characteristics in detail.

2. Thermo-responsive hydrogels

Among the possible environmental stimuli, the temperature is certainly the most widely used trigger to adjust the mechanical performance of hydrogels. Short response time, easy to operate, and adjustable transition temperatures account for its broad application. According to the toughening mechanisms, temperature-responsive, or more often termed as thermo-responsive hydrogels with stimulated mechanical performance can be classified into three main categories: hydrogels with polymer phase separation, hydrogels with glassy-like transition, and hydrogels with fusible links.

2.1 Thermo-mechanical response induced by polymer phase separation.

Phase transition in polymers plays a central role not only in the scientific understanding of condensed matter but also in their technological development.⁴⁹ In macromolecular

solutions or for swollen polymer networks, the solubility, and swelling properties, respectively, strongly depend on the polymer/solvent interactions. For a given binary system, polymer/solvent, these interactions vary with temperature and these variations can lead in certain cases to a continuous or discontinuous phase transition around a critical temperature.⁵⁹ Crossing the phase transition temperature (T_c), polymer solutions as well as covalent hydrogels experience a tremendous change in viscoelastic properties. Based on the change of their solubility with temperature, thermo-responsive polymers can be classified into two opposite categories: polymers with a Lower Critical Solution Temperature (LCST) or an Upper Critical Solution Temperature (UCST).

2.1.1 LCST-type thermo-responsive mechanical hydrogels

Although this is not really the phase transition temperature that can be predicted from the classical Flory-Huggins theory for polymer solutions, LCST is the most widely used thermal transition for polymer in aqueous media due to huge number of polymer/water systems that exhibit this behavior. The LCST is the critical temperature below which the components of the mixture are fully miscible for all compositions. Typically, the polymer chains, in the coil-state in water at low temperature, will collapse into a globular state above the transition temperature and aggregate to form a polymer-rich phase in equilibrium with a dilute polymer solution. Among the large amount of LCST polymers,⁶⁰ poly(*N*-isopropylacrylamide) (PNIPAm) is by far the most studied since the pioneering works on

the phase transition of gels in aqueous media.⁶¹ Due to its chemical stability, low toxicity,
low pH dependence,⁶² electroneutrality, and its LCST ($\sim 32^\circ\text{C}$) close to body temperature
and easily adjustable with comonomers, PNIPAm hydrogels have been considered for
many applications.

As a pioneering work, Takigawa et al.⁶³ demonstrated that Young's modulus of homo-
PNIPAm hydrogel was increased by more than one decade upon heating above T_c . During
phase separation, the PNIPAm chains self-associate and form a rich-polymer percolating
framework which serves as a load-bearing phase to increase gel stiffness, extensibility, and
toughness by enhancing energy dissipation (Figure 3a). A linear stress-strain behavior was
observed for PNIPAm hydrogel, both below and above the LCST, while later this linearity
was observed only at small strains.⁶⁴ Thereafter, many efforts were devoted to the thermo-
responsive toughening of PNIPAm hydrogels.⁶⁵⁻⁶⁷ Recently, by incorporating monomers or
other organic or inorganic compounds into the PNIPAm network (copolymers,⁶⁸
topological hydrogel⁶⁹⁻⁷¹ or nanocomposites⁷²) the resulting soft materials have
demonstrated thermo-toughening performance comparable to homo-PNIPAm hydrogels.
In these cases, the transition temperature of hydrogels can be finely tuned with the
incorporation of the other component, no matter chemically copolymerized in the PNIPAm
network or physically mixed,⁷³⁻⁷⁴ to meet the demand of specific applications. In this
context, the mechanisms of volume-phase transition in polymer gels have been intensively
discussed, both experimentally and theoretically, from the viewpoint of structure, dynamics,

kinetics, and equilibrium thermodynamics.⁷⁵ For more details, readers may refer to the recent review elsewhere.⁷⁶

During micro-phase separation, the coil/globule transition undergone at the molecular level by the elastically active PNIPAm chains usually gives rise to a macroscopic shrinkage of the gels, termed as “volume phase transition”.⁵⁰ Although this feature can endow the materials with potential applications in specific fields such as sensors and actuators, it hinders many practical perspectives relative to mechanical properties. For example, it is sometimes unnecessary or even undesirable to have a soft material that swells or shrinks during use. In addition, the volume contraction that accompanies the phase separation complicates the interpretation of the exact role of the two-phase morphology on the mechanical properties. It is indeed difficult to separate the intricate contributions of the phase separation and the change in polymer concentration.⁵⁰

To solve this puzzle, Guo et al. developed highly swollen networks with different topologies capable of undergoing phase separation with significant modification of their mechanical properties without any change of their macroscopic dimensions (phase transition in isochoric conditions). A first topology was designed by grafting hydrophilic poly(*N,N*-dimethylacrylamide) (PDMA) side chains on a thermo-responsive PNIPAm network (PNIPAm-*g*-PDMA gel or GPN-D) (Figure 3b). Above T_c , the thermo-responsive PNIPAm backbone phase separates and forms a concentrated load-bearing scaffold

accounting for less than 10% of the whole volume, while the swelling pressure of the hydrophilic PDMA side chains allows to maintain the high level of hydration of the gel avoiding any volume phase transition. As shown in Figure 3c, the gel effectively retains its original dimensions set by the preparation state on either side of T_c . Unlike conventional covalent bonds, the physical interactions between PNIPAm backbones triggered by the phase separation process have low selectivity and can easily break and reform, ensuring topological adaptation of the stretched network as well as a greater ability to dissipate energy. From small-angle neutron scattering (SANS), it was shown that this gel gave rise to a bi-continuous structure that aligned under loading at high temperature. By comparison with the mechanical properties at low temperature, at high temperature the hydrogels achieved fracture stress and an elastic modulus 10 times higher and extensibility twice as large (Figure 3d). The deformation of the rich-PNIPAm phase also leads to significant dissipative processes and high toughness (fracture energy $\sim 1000 \text{ J.m}^{-2}$). Interestingly, this was also the first time that an unusual crack bifurcation pattern has been reported in the field of hydrogels; such behavior having been observed mainly with natural rubbers (Figure 3e).

During subsequent works, it was shown that the mechanical performances of these thermo-responsive hydrogels were strongly dependent on the architecture of the networks.⁷⁷⁻⁷⁹ In particular, the length and density of hydrophilic grafts are crucial: shorter PDMA chains lead to much less pronounced fracture resistance, while higher graft density results in lower

fracture energy due to the lower fraction of PNIPAm domains (Figure 3f). By comparison, a hydrogel of opposite topology was prepared with the same PNIPAm/PDMA weight ratio (50/50) but this time by introducing PNIPAM grafts onto the crosslinked PDMA network (GPD-N gel). While exhibiting a similar phase separation process upon heating induced by PNIPAm side chains, this hydrogel showed much lower resistance to fracture than the previous GPN-D gel with no evidence of crack bifurcation.⁷⁷ From SANS experiments, a micellar architecture has been proposed with a swollen PDMA network physically crosslinked via PNIPAm aggregates. With this topology, the thermo-reinforcement increases with the size of PNIPAm sidechains, keeping constant the weight ratio PNIPAm/PDMA.⁷⁹ In fact, this strategy of reinforcement induced by a microphase separation process is somehow similar to that used in the case of nanocomposite gels where macromolecular chains are strongly anchored to the surface of inorganic particles.⁸⁰ The main difference, in the case of GPD-N gels, is that it is the chains of PNIPAm that self-associate to form their own reinforcement domains. In all cases, these organic or inorganic “fillers” act as additional crosslinkers increasing the elastic modulus but also the dissipation phenomena to pull off the chain either from the surface of the inorganic particle or from the polymer microdomain.

Compared to previous grafted architectures, other hydrogels such as semi-interpenetrated networks (semi-IPN) have also demonstrated similar thermo-responsive mechanical performance by forming comparable microstructure and giving rise to a similar mode of

crack propagation.⁷⁸ From a general point of view, the main characteristics of the thermo-reinforcement demonstrated with the grafted gels are reproduced with the semi-IPNs and the best properties are obtained with the semi-IPN prepared from a crosslinked PNIPAm network. It is therefore important to form during the phase separation a percolating network (here the crosslinked PNIPAm) as thick as possible which will play the key role of the load-bearing scaffold while keeping in mind that the hydrophilic counterpart remains important to preserve a high level of hydration at high temperature.

As the topology of hydrogels has a strong impact on thermo-responsive behavior, the precise construction of network structure is essential for the development of hydrogels with improved mechanical properties. Recently, Ida et al.⁸¹⁻⁸⁵ prepared a series of PNIPAm-based hydrogels by post-polymerization method, revealing that the type of copolymer network, the feed molar ratio, and the sequence of monomers effectively affected the hydrogel structure, the sharpness of the thermodynamic transition, and the mechanical properties. Well-designed amphiphilic structures with crosslinked PNIPAm domains were formed by post-crosslinking the end-blocks of triblock prepolymers with PNIPAm block either at the middle or at the ends. Compared to the hydrogels with a random sequence of monomers and crosslinkers with the same composition, Ida's hydrogels showed a faster and sharper volume phase transition upon temperature change as well as higher elastic modulus.⁸¹⁻⁸² Thermally responsive crosslinked PNIPAm domains collapse when heated and they act as fillers by dissipating energy and improving hydrogel toughness as

previously described. Interestingly, the amphiphilic hydrogels designed with these thermo-responsive crosslinked domains can be studied under the preparation state while preserving isochoric conditions on either side of the phase transition temperature. Under these conditions, it is possible to specifically analyze the impact of the phase transition on the elastic modulus and the extensibility during heating.⁸¹

While hydrogels derived from PNIPAm have drawn considerable attention to thermo-responsive toughening performance, some weaknesses remain. One of the major drawbacks of these gels concerns their relatively weak mechanical properties, in particular their low elastic modulus ($\sim$ a few tens of kPa) and fracture stress (< 100 kPa) even above the transition temperature. Moreover, while the PNIPAm chain undergoes a relatively sharp coil/globule transition on a small temperature scale,⁸⁶ the corresponding hydrogels undergo a much smoother and gradual mechanical toughening, giving rise to a large hysteresis between heating and cooling processes. This kinetic behavior is closely dependent on the rate of temperature change. It is mainly due to the low collective diffusion coefficient of PNIPAm chains forming the 3D network, as well as to a strong slowing down of their mobility during the formation of very concentrated domains.⁷⁴ This is the case for example with the fracture energy of GPN-D hydrogels which increases from 100 to 1000 J.m⁻² over a wide temperature range from 33 to 60 °C.⁸⁷

Figure 3. LCST-type thermo-responsive toughening of hydrogels. a) Schematic diagram representing the conformation of PNIPAm at different temperatures. The collapsed PNIPAm chains are defined as the load-bearing phase. Reproduced with permission.⁸⁷ Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. b) Schematic structure of thermo-responsive graft hydrogels GPN-D, GPD-N, and semi-IPN hydrogels GPN/PD, GPD/PN. Reproduced from⁷⁸ Copyright 2016 American Chemical Society. c) GPN-D gel is able to avoid

369 volume phase transition with relatively high hydration level (water content $\cong$ 83 wt%).
370 Reproduced with permission.⁸⁷ Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA,
371 Weinheim. d) Uniaxial tensile stress-strain curves of GPN-D at 20 °C and 60 °C. e) Photos of GPN-
372 D gels at 60 °C undergoing fracture test, which illustrate the crack bifurcation process.
373 Reproduced with permission.⁸⁷ Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA,
374 Weinheim. f) Fracture energies obtained with PNIPA/PDMA hydrogels at 60 °C. Reproduced
375 from⁷⁸ Copyright 2016 American Chemical Society.

376
377 Besides the thermo-responsive PNIPAm-based hydrogels which are by far the most studied,
378 other LCST-type hydrogels have also demonstrated similar toughening behavior in
379 response to the thermal trigger. Shibayama et al. have recently reported the synthesis and
380 characterization of poly(oligo-ethylene glycol methyl ether methacrylate)-based gels
381 prepared with two monomers having different ethylene oxide chain lengths ($n = 2$ and $n =$
382 $4-5$).⁸⁸ By changing the comonomer ratio, they were able to change the LCST of the
383 polymer network as well as the association process above the transition temperature
384 providing a large spectrum of elastic to viscoelastic transitions with temperature. Although
385 this study was carried out under isochoric conditions, giving rise to specific information on
386 the biphasic morphology, the analysis of the mechanical properties was limited to small
387 deformation. As reported with PNIPAm-based hydrogels,⁷⁷ the comparable shear modulus
388 obtained at small strain and high temperatures could hide large differences in fracture
389 energies (Figure 3f). Therefore, it seems important to systematically extend the analysis to
390 large deformations to deepen the mechanical characteristics of gels and in particular the

391 impact of dissipative processes on fracture phenomena. Indeed, while the previous reported
392 GPN-D hydrogel exhibits fracture energy 10 times higher than that of its GPD-N
393 counterpart of the same composition at 60 °C, they exhibit similar elastic behavior when
394 studied at small deformation.⁷⁸

395 2.1.2 Thermo-responsive mechanical properties of UCST-type hydrogels

396 In contrast to LCST type hydrogels, thermo-responsive polymer networks with an upper
397 critical solution temperature (UCST) can dissolve in solvents above the UCST and start to
398 phase separate below the UCST. In theory, many polymers show a UCST in a given solvent
399 due to complex temperature dependences of the interaction parameter.⁸⁹ The key is whether
400 the thermo-triggered phase transition takes place under gentle conditions as expected for
401 hydrogels (typically between 0-100 °C). UCST-type polymers, which are based on specific
402 interactions (hydrogen bonding and/or electrostatic interactions), can be mechanically
403 reinforced by cooling below T_c and weakened by heating above the transition temperature.
404 Compared to LCST-type hydrogels, UCST ones remain much less explored mainly due to
405 the few available polymer candidates.⁸⁹⁻⁹⁰

406 As a representative example of UCST-type polymers, poly(*N*-acryloylglycinamide)
407 (PNAGA) was discovered over half a century ago and widely used in supramolecular
408 chemistry.⁹¹ Upon heating, highly concentrated PNAGA solutions demonstrate interesting
409 mechanical performance with good stability and thermo-thinning properties.⁹² Interestingly,

410 by anchoring LCST-type PNIPAm side-chains to a UCST network of PNAGA, Guo et al.⁹³
411 have developed new thermo-responsive hydrogels with double temperature response. By
412 adjusting the composition between PNAGA and PNIPAm, it is possible to work in
413 isochoric conditions while exploring the two independent phase transitions (UCST and
414 LCST). As a result, the temperature range can be divided into three different domains: 1)
415 low temperatures ($T < \text{UCST}$ and LCST), 2) intermediate temperatures ($\text{UCST} < T <$
416 LCST), and 3) high temperatures ($T > \text{UCST}$ and LCST). In the case of this dual thermo-
417 responsive network, the mechanical modifications triggered by opposite phase transitions
418 are dissimilar. At high temperature ($T > \text{UCST}$ and LCST), the PNIPAm side-chains
419 collapse and self-associate into concentrated domains through hydrophobic interactions
420 coupled with intra- and inter-molecular hydrogen bonds. These strong interactions give rise
421 to the enhancement of both rigidity and extensibility as already described with hydrophilic
422 PDMA network grafted with PNIPAm side-chains. By comparison, the phase separation of
423 PNAGA at low temperature ($T < \text{UCST}$ and LCST) does not involve hydrophobic
424 interactions and the intra- and inter-chain associations related to the formation of hydrogen
425 bonds are weaker due to the stronger competition from water molecules for binding sites.
426 The phase transition of the PNAGA network leads to an increase of the Young modulus,
427 similar to that observed at high temperature with the phase transition of the PNIPAm chains,
428 but to a strain at break 10 times lower (Figure 4a). This clearly underlines the importance
429 of exploring the mechanical properties of gels at both small and large deformations. Indeed,

this feature may help to explain analogous phenomena reported with other UCST hydrogels, including zwitterionic⁹⁴ or neutral⁹⁵ systems. In addition to changes in mechanical properties, PNAGA-based dual thermally responsive hydrogels⁹⁶ also exhibit the obvious transparency variation upon temperature disturbing, which makes it possible as an electronic skin to qualitatively evaluate the ambient temperature (Figure 4b).

Figure 4. UCST-type thermo-responsive toughening of hydrogels. a) Schematic representation of thermo-responsive self-assembly and mechanical properties of PAN (NAGA monomer and PNIPAm) hydrogels upon temperature change. Figure colored for better illustration. Original in black and white. Reproduced with permission.⁹³ Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. b) Hydrogel as the robot's electronic skin to test different environment temperatures (refrigerator, room temperature, and oven). Reproduced with permission.⁹⁶ Copyright 2021 The Royal Society of Chemistry.

443

444 In addition to these synthetic systems, similar strategies have been developed on the basis
445 of single or double networks by coupling covalent bonds with physical interactions
446 involving bio-based molecules or polymers capable of self-associating by cooling. This is
447 the case for example with low molecular weight gelators combining guanosine, borax, and
448 potassium hydroxide which can form a supramolecular network within a covalent hydrogel
449 of PDMA,⁹⁷ with crosslinked polyacrylamide networks interpenetrated with agarose chains
450 which are known to reversibly form physical gels upon cooling⁹⁸⁻⁹⁹ or with covalently
451 cross-linked gelatin capable of forming additional physical junctions (triple helices) by
452 cooling.¹⁰⁰ All these studies have demonstrated that the formation of second physical
453 network results in a dramatic increase in strength and toughness at room temperature;
454 physical interactions making an essential contribution to the dissipation process. In these
455 cases, heating/cooling cycles have been mainly applied to promote mechanical recovery
456 after large deformations and self-healing properties rather than studying the variation in
457 mechanical properties throughout the thermal transition.

458 2.2 Thermo-responsive mechanical properties of hydrogels with glassy-like transitions

459 While thermo-softening hydrogels involving UCST polymers remain relatively rare,
460 thermo-softening materials are ubiquitous in nature. In the field of the polymer industry,
461 for instance, thermo-softening plastics, more usually termed thermoplastics, are widely

used for manufacturing a wide variety of items as they are easily pliable or moldable above their softening temperature and solidifies upon cooling. At the molecular level, the polymer segments initially in the frozen state acquire mobility when the temperature is raised above the glass transition temperature (T_g), switching the polymer materials from the rigid glassy state to the soft rubbery state.¹⁰¹ Without a doubt, this feature is not exclusive to non-solvent materials: a global group of researchers has attempted to apply this strategy in the preparation of thermo-softening hydrogels.

In recent years, Wu's group has designed a series of robust hydrogels following this strategy. As a typical example, ultra-stiff and tough hydrogels have been prepared by copolymerizing methacrylic acid (MAAc) and methacrylamide (MAAm) in water.¹⁰² Indeed, the strong interactions between acid and amide groups allow the formation of a dense and robust hydrogen bond network which gives the material temperature-dependent mechanical properties. Below the transition temperature (T_c), hydrogels display considerable stiffness due to the glassy behavior of the polymer phase, with a tensile stress of 4-11 MPa and strain of 400-600%. The sharp decrease in tensile stress detected above T_c gives these materials mechanical shape memory properties (Figure 5a). Later, the structure-properties relationships and the kinetics of the structure formation have been further investigated to reveal the mechanism of thermo-responsive toughening.¹⁰³ Moreover, systematic researches involving dynamic hydrogen bonds have been carried out to illustrate the concept of glass transition hydrogels as well.^{93, 94}

More generally, hydrogels with similar thermo-softening performance have been reported in other systems with various noncovalent interactions, such as hydrogen bonds,¹⁰⁴ hydrophobic interactions,¹⁰⁵⁻¹⁰⁶ and ionic bonds.¹⁰⁷⁻¹⁰⁹ For example, Wang¹⁰⁴ has reported thermo-responsive poly(vinylpyrrolidone-*co*-acryloxy acetophenone) glassy hydrogels with high tensile strength (8.4 MPa) and Young's modulus (94 MPa) at room temperature. When heated to 90 °C, the elastic modulus of gels decreased over more than 3 decades making this rigid hydrogel a suitable candidate as a shape memory material for surgical fixation devices to wrap around and support various shapes of limbs. In another study, hydrogen bonds, dipole-dipole, and hydrophobic interactions were coupled by copolymerizing acrylonitrile with N-acryloyl-2-glycine. These tough hydrogels clearly demonstrate thermo-softening performance when heated from 10 °C (Young's modulus 430 MPa) to 37 °C (Young's modulus 16 MPa). Due to the presence of carboxylic groups in the copolymer network, these hydrogels exhibit a shape memory responsive behavior, controllable by both temperature and pH, preparing them as attractive candidates for permanent embolic agents.¹¹⁰

While most of this work of hydrogels associates the temperature dependence of mechanical properties with the existence of a glass transition, as judged by the softening performance, it is still unclear whether this transition is really of the same nature as that reported with thermoplastics. For instance, the relaxation times under T_g in conventional thermoplastics are essentially much longer than the typical duration of an experiment or a numerical

simulation,¹¹¹ while for some of these so-called “glassy hydrogels” the relaxation time is fairly short (e.g. $\sim 1 \text{ s}^{102}$). Theoretically, hydrogels with glass transition behavior should generally be designed with high T_g hydrophobic polymers. However, scientists can effectively prepare tough hydrogels with rather low glass transition polymer networks, which also demonstrate a glassy-like transition. As a typical example, Liang et al.¹¹² ingeniously designed a body temperature-responsive hydrogel based on the copolymerization of hydrophobic 2-phenoxyethyl acrylate (PEA, T_g of polymer $\sim 16^\circ\text{C}$) and hydrophilic acrylamide. Within these hydrogels, the high fraction of hydrophobic monomers is responsible for the low content of water at equilibrium (less than 50 wt%), as the aggregation of PEA moieties provides a hydrophobic micro-environment for the adjacent amide groups which further stabilize their intermolecular hydrogen bonds. The scission of dynamic hydrogen bonds between acrylamide units by increasing the temperature is then responsible for the thermo-responsive performance. As shown in Figure 5b, the hydrogel exhibits very high tensile strength at low temperature along with a high yield stress and good extensibility, highlighting high energy dissipation. These mechanical properties are highly temperature-dependent: just after heating by hand for a few seconds, the hydrogel becomes weak without any distinct signature of yielding.

Similar to thermoplastics which weakens above T_g , all of the aforementioned hydrogels demonstrate thermo-softening performance, which precludes their use in applications which require high mechanical properties at elevated temperature. Although hydrogels

designed with LCST-type polymers are good candidates for improving mechanical properties by heating, the phase separation kinetics, as well as moderate mechanical performances, requires the system to be further improved. Recently, inspired by the molecular mechanism of thermally stable proteins, Gong et al.³⁰ developed a novel thermo-responsive hydrogel that undergoes ultra-rapid, isochoric, and reversible switching from soft hydrogels to rigid plastic-like material with increasing temperature. The materials were prepared from inexpensive and non-toxic poly(acrylic acid) (PAAc) hydrogels containing calcium acetate. The synergistic combination of hydrophobic and ionic interactions leads to phase separation by heating with a subsequent rubbery-to-glassy transition at higher temperature. Crossing the transition temperature, the material's stiffness, strength and toughness increased 1800-, 80-, and 20-folds, respectively, and a thin gel sheet could support a 10 kg weight (Figure 5c). This work may significantly broaden the scope of thermally stiffened polymer applications, such as for heat absorption or in protective sportswear.

Figure 5. Thermo-responsive hydrogels based on the glassy-like transition. a) Tensile stress-strain curves and yielding stress of poly(methacrylamide-*co*-methacrylic acid) (P(MAAm-*co*-MAAc)) gel at different temperatures. Reproduced from¹⁰² Copyright 2019 American Chemical Society. b) Photo illustration of body temperature-dependent mechanical strength and uniaxial tensile behavior of a poly(2-phenoxyethyl methacrylate-*co*-acrylamide) (P(PEA-*co*-AAm)) hydrogel with 60 mol% of PEA and 40 mol% of AAm (P60-A40). The sheet was rigid at a surrounding

temperature of 10 °C and could bear a 100 g weight without any obvious deformation. However, upon heating by two fingers, the hydrogel became soft and was gradually stretched by the loaded weight. Reproduced from¹¹² Copyright 2019 American Chemical Society. c) Mechanism of thermo-induced instant switching from soft hydrogel to hard plastic-like materials by polymerizing PAAc hydrogel in presence of calcium ions. Pictures show a load of materials at low and high temperatures, where the gels become significantly toughened up with increasing temperature. Reproduced with permission.³⁰ Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA.

2.3 Thermo-responsive mechanical properties of hydrogels with fusible links

As we know, crystalline materials are significantly softened by heating above their melting point. This first order thermodynamic transition has also been used to develop thermo-responsive hydrogels by introducing fusible links in the macromolecular architecture. In this context, several strategies have been considered: either from semi-crystalline networks or by adding crystalline additives.

A typical example of such hydrogels was prepared by copolymerization of crystallizable n-stearyl acrylate (SA) segments into a hydrophilic poly(acrylic acid) network. The mechanical properties of these materials exhibit a sharp temperature dependence when the temperature is raised above 50 °C with Young's modulus of hydrogels decreasing abruptly by about two orders of magnitude from 10^7 to 10^5 Pa.¹¹³ Based on Small-Angle X-ray Diffraction and Differential Scanning Calorimetry experiments, it was shown that the long

565 stearyl side-chains, which self-organize at room temperature into crystalline lamellae
566 aligned perpendicular to the main chain, undergo an order-disorder transition above 50 °C.
567 The melting of these lamellae is then the driving force of the macroscopic transition which
568 allows going from hard plastic to a soft and flexible material.¹¹⁴ Similar thermo-responsive
569 gels were prepared by Okay et al. through copolymerizing acrylic acid with 20-50 mol %
570 of crystallizable n-octadecylacrylate.¹¹⁵ In the network, hydrophilic segments provide
571 flexibility to the network while hydrophobic units pack to form crystalline domains that
572 render the material mechanically robust. These melt-processable hydrogels display very
573 high compressive strength (90 MPa) and Young's modulus (26 GPa) as well as shape
574 memory behavior and self-healing properties as expected for such associating systems. In
575 further work, it revealed that the mechanical performance of these semi-crystalline thermo-
576 responsive hydrogels is related to synthesis parameters, including the type¹¹⁶⁻¹¹⁷ and the
577 amount of the monomers,¹¹⁸ the methods of polymerization,¹¹⁹ the water content of the
578 hydrogels¹²⁰, and the amount of surfactant.^{115, 121}

Figure 6. Thermo-responsive hydrogels based with fusible links. a) Scheme and tensile stress-strain curves of virgin and healed biphasic synergistic gels (BSGs) at 20 °C and 60 °C. Reproduced with permission.¹²² Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. b) Photos of organohydrogels that exhibit nonswelling behavior in water or oil, and tensile stress-strain curves of organohydrogel at 20 °C, 55 °C, and 70 °C. Reproduced with permission.¹²³ Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

However, these strategies for preparing thermo-switchable mechanical hydrogels depend on relatively sophisticated molecular design and chemical modification. Although the properties of these hydrogels are rather promising, their method of preparation is far from optimal because it requires several steps with the synthesis in organic solvents, or in water using a large amount of surfactant, followed by a purification step in pure water to obtain

the hydrogels. To overcome this problem, Zhao and coworkers¹²² developed a one-pot strategy to synthesize biphasic synergistic gels, called organohydrogels, by in situ polymerization of oil-in-water high internal-phase emulsions; the oleophilic stearyl methacrylate acting as the oil phase (Figure 6a). The semi-crystalline behavior of closely packed micro-inclusions within the elastic hydrogel matrix not only greatly improves the mechanical properties of hydrogels, but also endows these materials with switchable mechanical behavior. As a result, these gels exhibit a broad spectrum of mechanical performance under tensile tests ranging from high modulus and low strain at break at 20 °C to low modulus and high strain at 60 °C. In further work, Liu et al.¹²³ applied this strategy using lauryl methacrylate as the oily phase, to prepare organohydrogels combining both high strain and tough shape memory properties. These biphasic materials can maintain isochoric conditions, both in water and in oil, and withstanding high load at different temperatures (Figure 6b).¹²³ During shape memory experiments, the material was shown to exhibit a high deformation capacity with fully recoverable deformation, both under stretch (up to 2600%) and under compression (up to 85%) by applying a load almost 20 times greater than the weight of the material. In subsequent studies, the introduction of supramolecular interactions (e.g., acrylic acid/ Fe^{3+}) in the hydrophilic phase showed that it was possible to prepare organohydrogels responding to two orthogonal stimuli: the temperature for the crystalline oily phase and addition of a competitor for the supramolecular interactions.¹²⁴

612

613 **3. Photo-responsive hydrogels**

614 Like temperature, light is another noninvasive trigger that allows remote, easy, and rapid
615 manipulation of materials without the need of additional reagents, and therefore with
616 limited byproducts.¹²⁵ Typically, the photo-responsiveness of hydrogels can be induced
617 either by the 3D polymer network itself or by inorganic additives incorporated therein.
618 While in the first case the photo-response generally leads to a variation in the degree of
619 crosslinking by photoreaction, the use of additives more generally involves an overall
620 photothermal response without variation in the degree of crosslinking.

621 **3.1 Light-responsive polymer networks**

622 Typical photoreactions of polymers include cleavage,⁴⁰ addition,⁴¹ exchange,⁴² and
623 isomerization.⁴⁴⁻⁴⁵ *O*-nitrobenzyl ester is a typical example of cleavage-type functional
624 groups that are currently used for the design of photo-responsive hydrogels.¹²⁵ For instance,
625 the photo-labile bond of the 2-nitrobenzyl functional group of the hydrophobic monomer
626 (2-nitrobenzyloxycarbonylaminoethyl methacrylate (NBOC)), can be irreversibly split
627 under UV irradiation with the formation of hydrophilic 2-aminoethyl methacrylate (AMA)
628 and the release of 2-nitrobenzaldehyde and CO₂.¹²⁶ Starting from a linear copolymer of
629 hydrophilic 2-ureidoethyl methacrylate (UM) and NBOC, poly(UM-*co*-NBOC), which

initially self-assembles through hydrophobic interactions between NBOC units, UV irradiation will cause a succession of chemical and physical events as follows 1) the transformation of hydrophobic NBOC groups into hydrophilic AMA units, 2) the disassembly of hydrophobic crosslinks and 3) the chemical reaction between amino groups of AMA and ester bonds of UM thus forming new chemical crosslinks.¹²⁶ As shown in Figure 7a, poly(UM-co-NBOC) hydrogels after UV irradiation exhibit a higher Young's modulus but lower failure strain and stress compared with those without UV irradiation. Due to the limited penetration thickness of UV, the hydrogel demonstrates a sandwiched structure with two rigid outer layers and a soft inner layer after UV irradiation. Under deformation, the outer layers fractured preferentially (like the first highly crosslinked network of a double network gel), while the inner layer maintained the whole integrity of hydrogels, playing a role resembling the second loosely crosslinked network of DN gels. By adjusting UV curing time and/or UV penetration length, the precise control of the sandwich structure can be finely achieved. The thinner the soft middle layer, the weaker the ability to bear the stretching and maintain global integrity.

Another elegant approach is to prepare hydrogels with photo-tunable crosslinking degrees via photo-addition reactions. Coumarin (COU), one of the well-known light-sensitive molecules, undergoes a [2+2] photo dimerization under irradiation at 365 nm while the resulting adduct can be decoupled by irradiation at 254 nm.¹²⁷ Sun et al.⁴¹ have first prepared linear polyacrylamides bearing pendant COU groups. In the presence of γ -

650 cyclodextrin (γ CD), which can host two molecules of COU, the initial polymer solution
651 was transformed into a transient network with the formation of dynamic COU- γ CD-COU
652 interchain bonds. After irradiation at 365 nm, the dimerization of the 2 COU molecules
653 hosted in the same γ CD cavity transforms the physical bond into a covalent bond which
654 results in stiffening of the network with a doubling of the storage modulus. In contrast,
655 when irradiated at 254 nm light, the chemical hydrogel turns back to a soft host-guest
656 physical network.

657 In contrast to photo-responsive toughening of hydrogels via the tuning of covalent bonds,
658 the possibility of using dynamic photo-reversible noncovalent interactions has been much
659 less investigated. Very recently, it has been reported that photo-sensitive coordinate bonds
660 can efficiently release the energy stored by the hydrogel.¹²⁸ The authors took
661 poly(acrylamide-co-acrylic acid) (P(AAm-co-AAc)) hydrogel for illustration. After being
662 prestretched and immersed in Fe^{3+} solution, the deformation of hydrogel is fixed by the
663 coordinate bonds between Fe^{3+} and carboxyl groups from AAc units which temporarily
664 store potential energy in hydrogels. After UV irradiation, Fe^{3+} is reduced to Fe^{2+} , resulting
665 in the breakdown of the coordinate bonds and the fast release of the elastic potential energy
666 stored in the hydrogel.¹²⁸ This strategy of storing and releasing elastic energy, based on the
667 destabilization of the coordination bonds by photoreduction, endows hydrogels with an
668 elasticity-plasticity switchability, multi-stable deformability in fully reversible and
669 programmable manners, and anisotropic or isotropic deformations. With the high power

670 density and programmability via this customizable modular design, these hydrogels
671 demonstrated potential for broad applications in artificial muscles, contractile wound
672 dressing, and high-power actuators. In the same manner, photo-responsive adhesion can be
673 easily achieved by tuning coordination bonds between Fe^{3+} and carboxyl groups.¹²⁹ Upon
674 irradiation, the dissociation of complexes causes a strong decrease in the adhesion energy
675 from 200 to 10 J m⁻².

676 However, the above photo-cleavage and addition reactions are generally not fully
677 reversible, which in some cases may limit the practical use of such materials.
678 Comparatively, the use of photo-isomerization reactions makes it possible to prepare
679 materials with satisfactory reversibility of their mechanical properties. Azobenzene, as a
680 photo-responsive molecule, undergoes trans-to-cis and cis-to-trans isomerizations upon
681 exposure to UV and blue light, respectively, resulting in a change of distance between the
682 two phenyl rings (from 9 Å to 5.5 Å) and dipole moments (from 0.5 D to 3.1 D) for trans
683 and cis isomers respectively. Hydrogels that incorporate photo-switchable molecules can
684 exhibit reversible variations in stiffness as a function of the irradiation wavelengths. These
685 stimuli-sensitive hydrogels are candidates to direct or probe osteogenic and myogenic
686 differentiation of human mesenchymal stem cells (MSCs).¹³⁰⁻¹³¹ It has been reported that
687 MSCs grown on substrates with varying stiffness express implicit changes, such as
688 development, aging, and fibrosis. Upon blue light (490 nm), the polyacrylamide hydrogel
689 containing 4,4'-diacrylamidoazobenzene becomes stiffer as the predominant trans isomer,

which is less polar, has a greater ability to self-associate. At the same time, cells exhibit a better spreading with larger spread cell areas in these stiffer hydrogel substrates compared to softer ones (Figure 7b).¹³² In a similar work, a peptide crosslinker containing azobenzene is introduced into poly(ethylene glycol) to form a light-responsive hydrogel. Upon irradiation with cytocompatible doses of 365 nm light (UV), isomerization to the azobenzene cis configuration leads to a softening of the hydrogel up to 100 – 200 Pa (shear storage modulus). The modulus of the gel can be well tuned upon irradiation with light with different wavelengths (Figure 7c). The planar trans conformation can better stabilize the hydrogen bonds between the peptide cross-linkers and harden the substrate.¹³³

Figure 7. Photo-responsive hydrogels with tunable mechanics. a) Schematic illustration “sandwich” structured hydrogels composed of poly(2-ureidoethyl methacrylate-co-2-nitrobenzyloxycarbonylaminoethyl methacrylate) (P(UM-co-NBOC)) (yellow part) and poly(2-ureidoethyl methacrylate-co-2-aminoethyl methacrylate) (P(UM-co-AMA)) (gray part) hydrogels. Tensile stress-strain curves and corresponding Young’s modulus (E) of the hydrogels before and after UV irradiation are shown on the right. The inset images are cross-sectional micrographs of the sample. Reproduced from¹²⁶. Copyright 2019 American Chemical Society. b) Young’s modulus of hydrogel after treatment and fluorescence microscopy images of mesenchymal stem cells (MSCs). Control gels (ctrl) that had not been exposed to UV. Blue gels were softened by exposure to UV (365 nm) irradiation for 30 min; (+) blue gels were exposed to blue (490 nm) light for 1 h, whereas (–) blue gels were unirradiated (left in the dark). Ctrl cells to be well spread, (–) blue cells to be smaller, and (+) blue cells to have recovered spreading. Reproduced from¹³². Copyright 2018 American Chemical Society. c) Isomerization of azobenzene (Azo) group and modulus of gels upon light. Reproduced from¹³³. Copyright 2015 American Chemical Society.

3.2 Light-responsive additives

Along with the hydrogels described previously, in which the photosensitive molecules belong to the architecture of the polymer network, photo-stimulation properties can also be generated using thermo-responsive polymers and photo-sensitive inorganic fillers. Among the systems investigated, near-infrared (NIR) often serves as a light trigger while gold nanoparticles or nanorods,¹³⁴⁻¹³⁵ ferrosferric oxide nanoparticles (Fe_3O_4 NPs),¹³⁶ and graphene oxide (GO)¹³⁷ are generally used as photo-convertor. In response to irradiation, part of the light energy is converted into thermal energy, which is referred to as the

723 photothermal effect. As an example, Huang and co-authors¹³⁸ developed light- and thermo-
724 responsive hydrogels by dispersing GO into interpenetrating networks formed by
725 physically cross-linked gelatin and chemically cross-linked polyacrylamide. Without light
726 irradiation, relatively high mechanical toughness (strength > 400 kPa and fracture strain >
727 500 %) was achieved by the double-network which dissipates energy through the sacrificial
728 gelatin network and GO particles bridging the two networks through supramolecular
729 interactions. Under the NIR trigger, temperature increases rapidly and causes the
730 dissociation of the thermo-responsive gelatin network which greatly declines the modulus
731 of the gel. With optimal content of GO and enough NIR time, hybrid GO-based hydrogels
732 display thermo-patterning and NIR irradiation erasing performances.

733 In another representative example, Wu and co-workers have developed stiff and tough
734 shape memory hydrogels responding to NIR light irradiation by incorporating gold
735 nanorods into a glassy gel matrix of poly(1-vinylimidazole-*co*-methacrylic acid)
736 hydrogels.¹³⁹ Owing to the photothermal properties of gold nanorods, the localized
737 temperature rise induced by the NIR light irradiation, which turns the hydrogel from rigid
738 to soft by crossing the T_g .¹⁴⁰ After irradiation and cooling to room temperature, the
739 hydrogels show an increase in Young's modulus (E), from 13 to 57 MPa, and yielding
740 stress (σ_y), from 0.6 to 2.1 MPa, whereas the water content decreases from 71 to 59 wt%
741 (Figure 8a). This behavior is attributed to the collapse of copolymer chains at high
742 temperature (above T_g) which leads to the formation of a denser network of hydrogen bonds

743 during cooling

744 The use of inorganic composite under light irradiation also proves to be an effective way
745 to tune the hydrophilic/hydrophobic balance of the material and consequently adjust the
746 mechanical properties of hydrogels. Recently, a sophisticated formulation of hybrid
747 materials was developed by Park and co-workers via loading in a poly(vinyl
748 alcohol)/chitosan matrix photocatalytic TiO₂/CD particles (CD for silica-carbon dots)
749 which exhibit a unique light absorption behavior with a wide UV-vis range of absorption
750 wavelengths. In that system, metal oxides TiO₂ produces a photoelectric effect under UV
751 activation, while the CDs demonstrate photoelectric properties due to the recombination of
752 photo-excited electron-hole pairs. Under UV or visible irradiation, the photocatalytic
753 nanomaterial changes the surface wettability of the thin-film hydrogel from hydrophobic
754 to hydrophilic due to reactive oxygen (O²⁻) and hydroxide species (–OH) which were
755 formed during the process. This hydrophilicity modification remarkably affects the
756 permeability to water which swells the hydrogel and therefore modifies its mechanical
757 behavior as well as its electronic properties (Figure 8b).

Figure 8. Photo-responsive hydrogels with tunable mechanics induced by embedded additives. a) Schematic and light responsive performance of poly(1-vinylimidazole-co-methacrylic acid) hydrogels integrated with 3 nM of gold nanorods. The tensile stress-strain curves and the corresponding Young's modulus (E) and yielding stress (σ_y), as well as the water content (q) determined as a function of irradiation time are shown on the right. Reproduced from¹³⁹. Copyright 2020 American Chemical Society. **b)** Scheme of the hydrogel thin-film based on titanium oxide (TiO₂) polydopamine-perfluorosilica carbon dot (CD)-conjugated chitosan-polyvinyl alcohol-loaded tannic acid along with UV and vis irradiation response affecting the surface hydrophilicity. The force-displacement curve and the swelling ratio of the hydrogel are shown on the right. Reproduced with permission.¹⁴¹ Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Although sharing various comparable advantages to the temperature stimulus, the light trigger is much less utilized, mainly due to the intrinsic feature of light. On one hand, upon

irradiation with relatively short-wave light such as UV, the short penetration depth is often a critical shortcoming.¹⁴² In certain cases, the high density also led to the degradation of the network's backbone.¹⁴³ On the other hand, relatively long-wave light such as NIR is often unable to provide enough energy to initiate photoreactions.

4. pH-sensitive hydrogels

pH-responsive hydrogels are a subset of stimuli-responsive systems capable of responding to pH environment. Weak polyelectrolyte hydrogels containing partially ionizable acidic units such as acrylic acid or methacrylic acid will become negatively charged with increasing the pH, typically above their pKa, and their counter-ions induce a huge increase of the osmotic pressure. On the other hand, hydrogels containing weak basic groups, like dimethylaminoethyl acrylate or 1-vinylimidazole, become cationic by lowering the pH.¹⁴⁴ As acidic or alkaline conditions have a significant impact on the strength of physical interactions, such as hydrogen bonds or ligand-metal coordinate bonds, they can be used to tune the macroscopic properties of hydrogels. In addition, the responsive ionization of networks at different pH also leads to significant volume change with osmotic pressure. This will greatly influence the mechanical properties of the hydrogels but in the following examples the impact of the physical interactions on the elastic properties is much greater than that linked to the variation in volume as given by $G \sim Q^{-b}$ with scaling exponent $b = 1/3$ in θ conditions and $b = 7/12$ in a good solvent.

4.1 Hydrogen bonds

A hydrogen bond is an electrostatic attraction between polar molecules that occurs when a hydrogen atom is bound to a highly electronegative atom such as nitrogen, oxygen, or fluorine.¹⁴⁵ These combinations are not stable enough, especially in aqueous media with pH disturbing. For instance, the deprotonation of -COOH in a basic environment leads to the breaking of the transient network of hydrogen bonds formed by the carboxylic groups.¹⁴⁶⁻¹⁴⁷

Zhang and co-authors reported a pH-sensitive and tough hydrogel composed of poly(1-vinylimidazole-*co*-acrylic acid) (P(VI-*co*-AAc)). The formation of intra- and inter-chain hydrogen bonds between the two monomers endows the gel with significant rigidity and strength at room temperature in a large range of pH ($3 \leq \text{pH} \leq 10$) (Figure 9a). The high stability of hydrogen bonds is related to the strength of the proton donor-acceptor pair.¹⁴⁸ However, the hydrogen bonds can be destructed, either in strongly acidic conditions by ionization of the imidazole function from VI, or under alkaline conditions with ionization of the carboxylic group from AAc. In such extreme conditions, the gels become much weaker. Similar behavior has been reported with other types of gels with strong hydrogen bonds.^{112, 149}

4.2 Metal-ligand coordinate bonds

810 In a coordinate bond, two electrons from one atom are supplied to a second atom to
811 generate the interaction. Many parameters, such as the electron-donating ability of the
812 ligand and the empty orbital of the central metal, govern the strength of the coordinate
813 bond. Similar to hydrogen bonds, metal-ligand coordinate bonds are typically vulnerable
814 to pH modifications as it dramatically changes the electron density of ligands or metals.

815 For instance, the ionization of carboxylic groups and the nature of coordination states
816 (mono-, bis-, or tris-ligand-metal complexes) are very sensitive to the pH environment,
817 which results in a variation of the association constants of carboxyl- Fe^{3+} chelates.^{37, 150}
818 Under weak acidic conditions ($\text{pH} = 4\text{-}5$), the tris-carboxyl- Fe^{3+} coordinate with the
819 highest stability constant dominates the association behavior and gives rise to the highest
820 stress at break (σ_b ; see Figure 9b), Young's modulus and extension work. On the other hand,
821 in more acidic environments ($\text{pH} = 1.7\text{-}3.5$), the swelling of the gels increases slightly,
822 while their mechanical properties decrease sharply, indicating the partial destruction of the
823 coordination complexes. Under extreme conditions, gels dissolve in highly acidic medium
824 ($\text{pH} \leq 1$) and disintegrate in alkaline solutions ($\text{pH} \geq 12$), forming ferric hydroxide
825 precipitates.³⁵ Analogous carboxylic coordination complexes have been reported with other
826 metals like Zr^{4+} ,¹⁵¹ Cu^{2+} ,¹⁵² Ag^+ ,¹⁵³ and Ca^{2+} .^{152, 154} For all these hydrogels, the mechanical
827 behavior remains closely related to the nature of the metal and that of the ionizable ligand,
828 as the stability of the coordinate bond strongly depends on the size of the cations.¹⁵⁴

4.3 Osmotic pressure change

In addition to the dynamic binding mechanisms mentioned above, when hydrogels carrying ionizable groups are exposed to acidic or alkaline conditions, they can undergo large variations in volume which strongly impact the mechanical performance.^{144, 146} In the case of PAAc hydrogels for example, the low level of swelling at low pH induced by the formation of hydrogen bonds between carboxyl groups makes the gels rather rigid and stable. Then, by increasing the pH above the pKa, the transformation of -COOH groups into carboxylate and counterions breaks the hydrogen bonds and generates a strong osmotic pressure leading to highly swollen and very soft gels which may eventually undergo autolysis. Although this is the general trend for weak polyelectrolytes up to moderate swelling, i.e. a Gaussian stretching regime characterized by a decrease of the modulus upon swelling, an abrupt upturn associated with non-Gaussian elasticity is observed for extremely larger swelling ratio > 100), i.e. smaller polymer volume fraction ($\phi_2 < 0.01$).¹⁵⁵ For the same reasons, the protonation at low pH of the nitrogen atom of dansyl groups, introduced by copolymerization within PAAm hydrogels, increases the swelling ratio by generating high osmotic pressure and therefore make the gels much softer and less stretchable.¹⁵⁶ Then, when the pH increases above pKa, the deprotonated and hydrophobic dansyl groups self-associate and act as dynamic crosslinks which improve the toughness of dansyl-based hydrogels (Figure 9c). Together with the pH and thermo-responsiveness induced by the host-guest complexes, the materials exhibit a triple-shape memory

849 performance.

850 Although pH is testified as an effective trigger for tuning the mechanical properties of
851 hydrogels, it is worth mentioning that this environmental trigger is less attractive compared
852 to temperature and light. One of the main reasons is that the response time is longer since
853 it requires the diffusion of solutes and solvent within the network and the volume variation
854 is generally quite large. Indeed, the rate of swelling, which is intrinsically linked to the
855 collective diffusion coefficient of the polymer, is also influenced by the characteristics of
856 the sample itself; in particular its size, shape, and porosity.¹⁵⁷ Another disadvantage of the
857 pH stimulus comes from implementation issues, which generally require a specific liquid
858 exchange to trigger the mechanical response.

Figure 9. pH-responsive hydrogels with tunable mechanical properties. a) Schematic illustration of the state of hydrogen bonds in poly(1-vinylimidazole-co-acrylic acid) (P(VI-co-AAc)) hydrogel equilibrated in aqueous solutions of different pH and their corresponding mechanical properties. Reproduced with permission.¹⁴⁸. Copyright 2017 Elsevier Ltd. b) Schematic representation of ligand-metal complexes formed uniaxial tensile properties of Fe^{3+} ions and poly(acrylic acid-co-acrylamide) (P(AAm-co-AAc)- Fe^{3+}) hydrogels with different feed ratios of AAc. The mechanical properties of hydrogels with AAc feed ratio of 15 mol% incubated in solutions at different pH are shown on the right side. Reproduced from³⁵ Copyright 2016 American Chemical Society. c) Chemical structure and uniaxial tensile properties of PAAM-based copolymeric hydrogels with dansyl side chains at different pH. The x, y and t are 10%, 6%, 10%, respectively. Chemical

structure slightly modified for better presenting the azobenzene group. Reproduced with permission.¹⁵⁶ Copyright 2016 The Royal Society of Chemistry.

5. Salt-responsive hydrogels

In nature, inorganic ions are involved in numerous tasks. For instance, the influx of sodium ions into the cytoplasm and the diffusion of calcium ions into muscle fibers lead to the contraction of our muscles. Mimicking nature, hydrogels may undergo mechanical change when in the presence of inorganic salt. Indeed, the salt may play versatile functionalities in tuning hydrogels' rigidity, including affecting coordinate bonds, impacting polymer solubility, shielding ionic bonds, and controlling osmotic pressure.

5.1 Influence of coordinate bonds

In chemistry, coordinate bonds typically involve the binding of a metal to certain ligands such as carboxylate-ions to form coordination complexes. These coordination complexes are of both academic and practical interest. In the case of hydrogels having a certain amount of coordinate sites, the introduction of suitable transition metal ions can give rise to the formation of new crosslinking points and effectively affect the mechanical performance of the hydrogels. It should be noted that the toughening process induced by the formation of strong metal-coordinate bonds is limited to specific ion pairs, which can be generally explained by the classical hard-soft acid-base theory postulating that hard acids bind

889 strongly to hard bases and soft acids strongly bind to soft bases.¹⁵⁸

890 As a representative example, Chen et al.¹⁵⁹ introduced Fe^{3+} into a double network gel
891 consisting of an agar gel, as the first physical network, embedded into a chemically
892 crosslinked second network of P(AAm-*co*-AAc) (PAMAAC). Besides the pH-tunable
893 performance derived from the AAc group, the gel demonstrates significant ion-
894 responsiveness. Compared to the gels without Fe^{3+} , Agar/PAMAAC- Fe^{3+} gels demonstrate
895 an enhancement of fracture stress and hysteresis energy by 3.4 times and 2.8 times,
896 respectively (Figure 10a). The large amplitude of the hysteresis comes from the unzipping
897 of the additional physical network of coordinate complexes.¹⁶⁰ Therefore, the formation of
898 reversible sacrificial ionic crosslinks appears as an interesting strategy to reinforce gel
899 properties by simply immersing polycarboxylic acid hydrogel into a suitable multivalent
900 salt solution.¹⁶¹

901 Metal ions can also significantly affect hydrogels' toughness by forming different dentate
902 ligands in coordination compounds;¹⁶² the mechanical properties being influenced by the
903 immersing time as well as the ion concentration. For example, poly(acrylonitrile-*co*-2-
904 methacryloyloxyethyl phosphorylcholine) (P(AN-*co*-MPC)) hydrogels, designed with
905 dipole-dipole interactions between cyano groups (CN-CN pairs) and coordinate bonds
906 between CN and Zn^{2+} ions, were developed by Han et al.³⁴ As shown in Figure 10b, the
907 hydrogel, which is initially reinforced by the strong CN-CN interactions within the network,

908 shrinks progressively when immersed in ZnCl_2 solutions as zinc ions may serve as
909 additional physical crosslinks between cyano groups due to favorable formation of
910 $\text{Zn}(\text{CN})_2$. Concurrently, the Young modulus increases from 7 MPa, initially in water, up to
911 38 MPa in 30% ZnCl_2 solution. Then, when the zinc ion concentration is increased beyond
912 30%, excessive zinc ions bind to single CN groups and shield other cyano groups from
913 forming dipole-dipole interactions. In this range of concentrations ($[\text{ZnCl}_2] > 38\%$), the gel
914 highly swells and its Young's modulus sharply decreases up to 0.05 MPa in 50 % ZnCl_2 .
915 Therefore, by adjusting the concentration of ZnCl_2 in the external solution, the authors
916 demonstrate that the elastic modulus of the gel can be tuned over a very wide range, from
917 kPa to MPa, allowing shape memory properties to be developed with various temporary
918 and permanent shapes.

Figure 10. Mechanism and mechanical properties of hydrogels with salt-responsiveness. a) Loading-unloading curves and the corresponding dissipated energies of Agar/PAMAAc-Fe³⁺ DN gel, Agar/PAMAAc DN gel, and PAMAAc-Fe³⁺ gel. Reproduced from¹⁵⁹ Copyright 2016 American Chemical Society. **b)** Schematic representation of 3 different hydrogel states featuring: i) CN-CN + CN-Zn interactions, ii) CN-CN interactions and iii) dissociation of the previous interactions of poly(acrylonitrile 2-methacryloyloxyethyl phosphorylcholine) hydrogel (named PAM in the figure) in response to zinc ions. On the right side, the figure shows the variation of Young's modulus (square $\square$) and the diameter (diamond $\diamond$) of the gel for different concentrations of ZnCl₂ (MgCl₂ solution serves as a control). Reproduced with permission.³⁴ Copyright 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Similar performances have been demonstrated in polycarboxylate systems with other metal

ions including Ca^{2+} ,^{152, 154, 161, 163-164} Al^{3+} ,¹⁶³ and Cu^{2+} ions¹⁵². Such behaviors are highly related to the type of central metal and ionizable ligand, as the bond stability fundamentally scales with the decreasing size of the cation.¹⁵⁴ Moreover, Zr^{4+} ions which are known to form coordinate bonds with sulfonate groups, can effectively reinforce such hydrogels.¹⁶⁵ For instance, the immersion of a poly(acrylamide-*co*-2-acrylamido-2-methyl-1-propanesulfonic acid) (P(AAm-*co*-AMPS)) hydrogel into a ZrOCl_2 solution gives rise to an enhancement in fracture stress of 3 orders of magnitude (from 2.5 kPa to 6.3 MPa). Upon stretching, the sulfonate- Zr^{4+} coordination complexes can break, dissipating energy, and reform, ensuring satisfactory mechanical performance. Owing to the dynamic nature of the coordinate bonds, these hydrogels show rate- and temperature-dependent mechanical performances, as well as good self-recovery properties. These hydrogels enable versatile applications in the biomedical and engineering fields, such as artificial tubular grasper.

5.2 Solubility effect

Besides the aforementioned mechanisms, salt can also modify the characteristics of hydrogels by affecting the polymer/water interactions. Historically, Hofmeister was the first to report that the water solubility of proteins could be increased or decreased in a controlled manner by adjusting the nature and concentration of the salt. Nowadays, the ranking of the physical properties of ions in aqueous solutions, known as Hofmeister series, is a benchmark widely used to modify the solubility of polymers and smaller molecules in

water.¹⁶⁶ Although the underlying mechanisms are still under debate after more than one century, hydrogen bonding, dispersion interactions, hydration forces, or even dissolved gas have been suggested for this phenomenon.¹⁶⁷ In the case of PNIPAm gels, for which interactions in water result from a compromise between hydrogen bonds and hydrophobic interactions, the transition temperature as well as the macroscopic properties can be finely tuned by applying the so-called Hofmeister effects.¹⁶⁸

In the Hofmeister series, ions are divided into “kosmotropes” and “chaotropes” with salting-out and salting-in effects, respectively, indicating how the interactions of small solute molecules with water affect the solubility of large molecules.¹⁶⁹ While the salting-out effect tends to reduce the hydration of polymer chains,¹⁷⁰ strengthen specific physical interactions,¹⁷¹ and consequently reinforce the mechanical behavior of hydrogels, the salting-in leads to opposite effects. In the work of Chen and co-authors,¹⁷² the mechanical properties of poly(acrylamide)/methylcellulose (PAAm/MC) hydrogels were significantly improved by simply soaking the gel in solutions of kosmotropic ions. By increasing the hydrophobic interactions, the small kosmotropic anions thus led to chain bundling, endowing the hydrogels with enhanced mechanical properties. For instance, the tensile strength of the treated hydrogel reached as high as 4.4 MPa, which is more than 30 times higher than that of the original hydrogel. Upon stretching, these hydrophobic associations readily break, dissipating energy, and then reform guaranteeing good mechanical performance. Following this strategy, the mechanical properties of these hydrogels can be

971 further tuned by varying the post soaking time and the kind of Hofmeister salts. The
972 PAAm/MC hydrogels treated with solutions of strong “salting-out” anions like Cit^{3-} , CO_3^{2-}
973 and SO_4^{2-} , reached higher compression strength of 27.6, 19.6, and 14.2 MPa, respectively.
974 In comparison, the same gel immersed in a solution containing a weak “salting-out” anion
975 (Cl^-) exhibits a much weaker fracture compression stress (7.4 MPa). While the high
976 mechanical performance of this hydrogel is maintained in saline solution, the hydrogel
977 swells and loses its mechanical strength when immersed in pure water.¹⁷² Very recently, He
978 and coauthors attested that the mechanical properties of poly(vinyl alcohol) (PVA)
979 hydrogels can be well-tuned at a broad range by simply soaking the as-prepared gels in
980 different ions solutions.¹⁷³ As shown in Figure 11a, hydrogen bonds forming or breaking
981 can be induced by ions due to the salting-out effect or salting-in effect. With different media
982 soaked, the PVA hydrogels demonstrate tensile strength from 50 kPa to 15 MPa, toughness
983 from 0.0167 to 150 MJ m^{-3} , and Young’s modulus from 24 to 2500 kPa (Figure 11b). It is
984 verified that the Hofmeister effect accounts for this phenomenon by affecting the
985 aggregation states of the polymer chains and the formation of structures, rather than just
986 affecting the hydration level or playing a role as the components of hydrogels. The
987 Hofmeister effect becomes more pronounced with crystalline hydrogels as the salt also
988 affect the crystalline degree in PVA hydrogels.¹⁷⁴

989 The salt-sensitive mechanical response of hydrogels can also be finely adjusted by simply
990 controlling the immersion time. Cui et al.¹⁷⁵ have developed chitosan/poly(acrylic acid)

991 double network nanocomposite hydrogels (CS/PAA/TA@CNC) via in situ polymerization
992 of acrylic acid in chitosan acid aqueous solution with tannic acid-coated cellulose
993 nanocrystal acting as nanofillers. These nanocomposite hydrogels were then soaked into a
994 saturated NaCl solution in order to aggregate chitosan chains by shielding electrostatic
995 repulsions between positively charged amino groups. Compared with the original hydrogel,
996 without soaking treatment, the “CS/PAA/TA@CNC-60” gel, which was immersed for 60
997 min in a saturated NaCl solution, exhibits a significant enhancement of the mechanical
998 properties with a 10-fold increase in the fracture stress and a 2-fold increase in the fracture
999 strain, which is attributed to a higher crosslinking density of chitosan induced by chain
1000 entanglement and salting-out effect (Figure 11c). With further extended soaking time, the
1001 fracture energy and elastic modulus began to decrease due to excessive shielded
1002 electrostatic repulsions, which has another salt effect will be discussed in the following
1003 part.

Figure 11. Mechanism and mechanical properties of hydrogels with Hofmeister effect. a) Hydrogen bonds form or break between PVA polymer chains induced by ions due to salting-out or salting-in effect. **b)** Strengths, toughness, and moduli of PVA hydrogels tuned by various anions (with Na^+ as the constant counterion); different cations (with Cl^- as the constant counterion); and Na_2SO_4 with concentrations ranging from 0 m to saturated. Reproduced with permission.¹⁷³ Copyright 2021 Wiley-VCH GmbH. **c)** Tensile stress–strain curves, elastic modulus, and energy-to-break of the tannic acid-coated cellulose nanocrystal CS/PAA/TA@CNC DN nanocomposite hydrogels with different soaking time in saturated NaCl solution. Reproduced from¹⁷⁵. Copyright 2019 American Chemical Society.

5.3 Shielding of ionic interactions

In hydrogels, ionic interactions greatly contribute to strengthening their properties. Upon stretching, these noncovalent bonds can reversibly break to dissipate energy and reform to guarantee their mechanical performance and stability. Consequently, the addition of small molecular salts can effectively screen the attractive interactions between oppositely charged groups carried by macromolecular chains, leading to the release of entangled polymer chains.^{39, 175}

Polyampholytes (PA) hydrogels, containing both anions and cations in their macromolecular structure, are typical examples of materials sensitive to salt additives due to electrostatic screening. In the pioneering work of Gong et al.,¹⁷⁶ PA hydrogels were prepared with an equal amount of the 3-(methacryloylamino) propyl-trimethylammonium chloride (MPTC, cationic monomer) and sodium p-styrenesulfonate (NaSS, anionic monomer). Close to the charge balance in pure water, these hydrogels display extremely high toughness with remarkable viscoelasticity which is attributed to the very wide distribution of ionic bond strengths. The strong bonds serve as permanent crosslinks, imparting elasticity, while the weak bonds reversibly break and reform, dissipating energy. However, the addition of inorganic salt gradually weakens the strength of electrostatic interactions and leads to a significant decrease in Young's modulus (from 2.2 to 0.1 MPa) and fracture stress σ_b (from 2.60 to 0.07 MPa). Unlike the intrachain ionic complexation that takes place in PA hydrogels, polyion complex (PIC) hydrogels prepared from equal

oppositely charged homo-polyelectrolytes can only lead to interchain complexation between polymers in the extended coil conformation. This interchain complexation, which takes place even at low polymer concentrations, greatly promotes the chain entanglement and the stability of ionic complexes, thus making the mechanical properties much superior to those of PA hydrogels with the same rate of combination of monomers. When these PIC hydrogels synthesized from MPTC and NaSS homopolymers are immersed in saline solutions of increasing concentration, a decrease in the breaking stress as well as a significant increase in fracture strain are observed (Figure 12a).¹⁷⁷ By tuning the screening of interpolymer electrostatic interactions with salt, it is possible to control the dynamics of ionic bonds and endow the hydrogel with self-healing properties. For instance, after soaking two pieces of hydrogels for 2 minutes in 3M NaCl and bringing them into contact for 12 hours at room temperature, the self-healed sample exhibits a recovery rate of 66 % in terms of work of extension with high strength (modulus $\sim$ 4.5 MPa; fracture stress $\sim$ 2.2 MPa; fracture strain $\sim$ 630%).

5.4 Controlling osmotic pressure

In hydrogels, water plasticizes polymers by disrupting chain interactions, creating free volume in the polymer network, enhancing chain mobility, and softening the material. The ionic contribution to the osmotic pressure has a huge effect on the swelling properties of gels and it can be used either to generate super swelling properties, as in superabsorbent polymers or to cause the gel collapsing when the excess of ionic pressure inside the network

is counterbalanced by that of the external environment with the addition of salt. Such osmotic deswelling, which increases the density of polymer chains in the network, also participates in strengthening the specific physical interactions.

This phenomenon has been particularly investigated in ionic gels using additional noncovalent associations as nicely exemplified by Gong and coworkers who couple electrostatic and hydrophobic interactions within the same network.¹⁷⁸ As shown in Figure 12b, the authors synthesized copolymers through cation- π complex-aided free-radical polymerization between an aromatic monomer and a cationic one. While the copolymer itself is water-soluble, due to electrostatic repulsions between the chains dominating the solution behavior, the addition of salt favors the formation of a gel coacervate as salt ions screen long-range electrostatic repulsions and strengthen the effective cation- π and hydrophobic interactions taking place intra- and inter-molecularly (Figure 12c). While the copolymer solution prepared in pure water is not sufficiently elastic to be able to withstand deformation, the system becomes much harder and more stretchable in salty environments (Figure 12d). Such materials, which are also characterized by self-healing and adhesive properties in saline conditions, are promising systems paving the way for the development of responsive hydrogels in physiological and marine environments.

Figure 12. Salt-sensitive hydrogels with shielding of ionic interactions and controlling osmotic pressure. a) Schematic illustration of PIC hydrogels prepared from poly(3-(methacryloylamino) propyl-trimethylammonium chloride) (MPTC) and poly(sodium p-styrenesulfonate) (NaSS) and uniaxial performance in response to immersion in different NaCl solutions. The chemical structure of corresponding monomers is illustrated on the left side. Reproduced with permission.¹⁷⁷ Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. b) Schematic illustration of design strategy with chemical structures of typical monomers used, c) fracture stress, fracture strain and elastic modulus obtained from stress-strain curves with

P(ATAC-adj-PEA) gels, and d) schematic illustration of the formation of coacervate in saltwater. Reproduced with permission.¹⁷⁸ Copyright 2019 Nature.

As already discussed, the introduction of salt which will favor the formation of physical-crosslinked domains largely contributes to the energy dissipation and endow the gels with reinforced mechanical performance.¹⁷⁹ Using the simple soaking process, salt-responsive hydrogels prepared from natural or synthetic macromolecules can be easily strengthened for use in versatile applications, such as bone regeneration,³³ tubular graspers,¹⁶⁵ sensors.¹⁷⁵ Nevertheless, as discussed in the case of pH-sensitive hydrogels, the time required for the solutes to diffuse within the gel can be a significant obstacle for some practical applications.

Conclusion and perspective

Over the past 4 decades, hydrogels with responsive properties have been definitively a hot topic with significant academic developments. Until the 1990s, researchers mainly focused on the thermodynamic aspects of the volume phase transition of hydrogels in response to environmental stimuli, and many new and complex architectures have been designed and studied within this framework. Since the beginning of the new century, the vast knowledge acquired on these systems, as well as the development of experimental techniques, have led to direct research towards the mechanical properties of hydrogels in order to elaborate smart and efficient reinforcement strategies. This new orientation, stimulated in particular by the potential of these swollen materials in biomedical applications, has led to a

1101 multiplication and a sophistication of the systems studied, making it possible to consider
1102 the control of their mechanical properties using single or multiple environmental triggers.
1103 Today, there is a truly solid basis of knowledge for the structure/properties relationships of
1104 smart hydrogels characterized by responsive mechanical properties under thermal, light,
1105 pH, and/or salt triggers, but improvements are needed and we have still a lot to learn from
1106 nature.

1107 In the case of stimuli-responsive gels, not only thermodynamics prevails but also kinetic
1108 aspects play an important role at different scales that must be considered in the transition
1109 process. On the one hand, the rate of thermal transfer is faster compared to the other
1110 processes (e.g. $2\text{--}3 \cdot 10^{-3} \text{ cm}^2 \cdot \text{s}^{-1}$ for PNIPAm). On the other hand, the transport rate of
1111 solvent or solute into or out of the network is much slower. In the case of a purely diffusive
1112 mechanism, the experimental values measured in the gels are close to the self-diffusion
1113 coefficients of the molecules (e.g. $2.6 \cdot 10^{-5} \text{ cm}^2 \cdot \text{s}^{-1}$ for D_2O). Moreover, the movement of
1114 polymer chains further limits the kinetic process in the case of large volume phase
1115 transition. On average, the collective diffusion coefficient for a homogeneous gel is around
1116 2 orders of magnitude lower compared to the solvent and 4 orders compared to the thermal
1117 stimulus. In particular, this factor will be the limiting step of the kinetic process in the case
1118 of large volume phase transition, keeping in mind that the characteristic swelling time (τ)
1119 scales with the square of the size of the sample (r) as: $\tau \sim r^2/D_0$. Such kinetic issues can
1120 be critical in the case of pH and/or salt responsive toughening, where environmental

modifications should be driven by soaking the gel in an external medium and waiting for minutes or even hours depending on the size of the sample. This is rather long compared to hydrogels found in the human body that display much shorter characteristic times on the order of a second or less. Photo-stimulation is an alternative a good way to overcome the problems associated with the slow diffusion of solutes into the gel, but the short penetrability of light remains a critical issue. Another problem that deserves to be pointed out concerns the sensitivity of the gel to a stimulus. Indeed, while in nature an infinitesimal change in biological signals can induce a significant mechanical response, synthetic responsive hydrogels require a greater variation in environmental conditions to provide a macroscopic response. In addition, the lack of reversibility of some responsive hydrogels also limits their long-term use.

With an increasing understanding of the structure/property relationships of these soft and wet materials, new versatile systems will certainly emerge in the future. On the one hand, an increasing number of smart hydrogels whose mechanical performances are responsive to novel stimuli may come on the scene, e.g. the electrical, magnetic, touch, or electrochemical triggers. These input signals are ubiquitous in bio-tissues, such as our central nervous system takes the art of electrochemistry for nerve conduction and muscle movement control. Different from currently applied triggers, these new stimuli may safely overcome the existing problem of low responsive time. Although hydrogels with such stimuli become increasingly valued in recent years, the related researches are still in their

1141 infancy compared to the real cases in nature. On the other hand, new hydrogels with
1142 stimuli-responsive mechanical performance may appear with a super-low threshold value.
1143 Furthermore, the gels may even become capable to differentiate between similar inputs.
1144 These perspectives are highly challenging for existing hydrogels but out of question in the
1145 biological world. For example, the motion of our smooth muscle is closely associated with
1146 very tiny environmental pH variation and the physiological effect of sodium and potassium
1147 ions are poles apart. Another important issue is how to create hydrogels with step-by-step
1148 regulation in mechanical performance. Taking the *Mimosa Pudica* for illustration: upon
1149 touching, the plant experiences stimulus perception at first, giving rise to electrical signal
1150 transmission in the next and finally induces rapid mechanical movement. The more intense
1151 the stimuli, the longer it takes to maintain the closing state. The advantage of this cascade
1152 system is that it is able to produce fast, delicate, adaptive, and reversible mechanical output.
1153 Nevertheless, there is still a certain distance before obtaining this kind of artificial soft
1154 matter.

1155 Indeed, after 40 years of intensive studies on responsive hydrogels, we have learned a lot
1156 about how to use physical interactions to control the macroscopic response of the hydrogel
1157 and in particular how to modulate the mechanical properties. Although we still have a long
1158 way to go by learning from nature, the weaknesses of current hydrogels will be the next
1159 milestones for future research with an increasing focus on practical applications in the near
1160 future.

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1172 **Notes**

1173 The authors declare no conflict of interest.

1174

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