Aggregated structures and their functionalities in hydrogels

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Funding information
Japan Society for the Promotion of Science, Grant/Award Numbers: JP17H06144, JP19K23617

Abstract
Biological soft tissues and hydrogels belong to the same category of soft and wet matter. Both of them are composed of polymer network and a certain amount of water, and permeable to small molecules. Biological tissues possess elaborated structures and exhibit outstanding functionalities. On the other hand, hydrogels are usually amorphous with poor functionality. In recent years, various hydrogels with robust functionalities have been developed by introducing aggregated structures into the gel networks, widely extend their applications in diverse fields, such as soft actuators, biological sensors, and structural biomaterials. Four strategies are usually used to fabricate aggregated structure into hydrogels, including molecular self-assembling, microphase separation, crystallization, and inorganic additives. Different aggregated structures entail the gel very different functionalities. A simple aggregated structure is able to bring multiple functionalities and a combination of them. These robust functionalities make the hydrogels diverse applications, such as soft actuators, biological sensors, and structural biomaterials.

This review attempts to emphasize the close relationship between aggregated structure and functionality of hydrogels. For this purpose, this paper is organized as follows. We will first introduce the strategies used for fabricating aggregated structures in hydrogels. The aggregated structures defined here include the self-assembling structures formed by natural or synthetic molecules, the microphase separation and crystallization of polymer network or fillers, and the organic or inorganic additives. Then, we will give an example to show that, by incorporating unidirectionally aligned lamellar

INTRODUCTION

In nature, living organisms provide the best demonstration of designing materials with well-defined hierarchical structure and elaborate functionality. For example, muscle is a soft tissue in most of animals to produce force and motion, and this function is closely related to its structure, which is composed of protein filaments of actin and myosin that organize into a liquid-crystalline structure.1 Another example is chameleons, which are distinguished by their ability to change skin color to adapt for environmental stimuli.2,3 Chameleons have a skin layer composed of cells with guanine nanocrystals and are able to tune the guanine nanocrystal lattice for the skin color change. Living organisms contain a large amount of water in their bodies, and these functionalities are achieved in a soft and wet gel-like state, through the well-organized structures with deformability. Creating artificial materials with similar structures and functionalities as natural materials is a grand challenge for material scientists. Hydrogels are ideal candidate for constructing such materials. Hydrogels are a type of materials composed of a crosslinked polymer network and abundance of water, which share similar soft and wet nature as biological tissues. However, conventional synthesized hydrogels are swollen polymer networks in water, and they are usually amorphous, weak, and with poor functions.4,5 In recent years, great success has been achieved in fabricating functional hydrogels by implementing aggregated structures into the gel network. The aggregated structures include the structures formed by either the polymer network itself6 or the organic and inorganic additives.7 The aggregated structures endow hydrogels robust functionalities, such as structural color,8 stimuli-responsive ability,9 mechanical strength,10 or a combination of them.11 These robust functionalities make the hydrogels diverse applications, such as soft actuators,12 biological sensors,13 and structural biomaterials.14

This review attempts to emphasize the close relationship between aggregated structure and functionality of hydrogels. For this purpose, this paper is organized as follows. We will first introduce the strategies used for fabricating aggregated structures in hydrogels. The aggregated structures defined here include the self-assembling structures formed by natural or synthetic molecules, the microphase separation and crystallization of polymer network or fillers, and the organic or inorganic additives. Then, we will give an example to show that, by incorporating unidirectionally aligned lamellar
bilayers into a simple gel network, the hydrogels have multiple functions, such as visible structural color, stress/strain response, 1D swelling, anisotropic molecular diffusion, anisotropic modulus, self-recovery, and excellent mechanical performance. After that, the effect of aggregated structures on structural color and fast thermal responsive behavior will be discussed in detail, due to their importance on biological sensing and soft actuators. Further, we will talk about the role of aggregated structure on mechanical performance, as a high mechanical performance is required in many applications of hydrogels, especially in using as structural biomaterials. Finally, the nonequilibrium aggregated structure in constructing human-like dynamic memorizing-forgetting hydrogel will be introduced.

**AGGREGATED STRUCTURES USED IN FABRICATING FUNCTIONAL HYDROGELS**

There have been many efforts toward developing aggregated structures in hydrogels. In general, they can be divided into four groups according to the fabricating strategy: molecular self-assembling, microphase separation, crystallization, and inorganic additives (Figure 1). Molecular self-assembling through weak noncovalent interactions has been widely used for fabricating aggregated structure in hydrogels. The noncovalent interactions used include ionic interaction, hydrophobic interaction, \( \pi-\pi \) stacking, and hydrogen bonding. The molecules used include natural and synthetic molecules. Natural molecules, such as DNA, chitosan, cellulose, and alginate, can be triggered to self-assemble by cooling or adding salts, polycations, or bases. For example, gelatin molecules form triple helical sequence upon cooling to about 30°C and aggregate as a network. Due to the inherent biological origins, these hydrogels usually have bioactivity, biocompatibility, and biodegradability, which are outstanding systems for biomedical applications. Synthetic rigid polymers are another type of molecules that are commonly used in constructing hydrogels with aggregated structures. For example, rigid polyanions in polycationic hydrogels can form various superstructures with length ranging from submicroscale to mesoscale and even macroscale, by controlling the localized orientation of rigid molecules. In addition, liquid crystalline molecules and block polymers are also usually involved in self-assembling in hydrogels. Microphase separation refers to the phase separation with phase structures in microscopic length scale, which is particularly relevant for living organisms. Biological tissues can be considered as a state of liquid–liquid microphase
separation. Some microphases that are enriched in molecules and some microphases that are depleted. The interface of these microphases forms a boundary, which allows the selective passage of some molecules but not others. These individual microphases also act as compartments with different physical properties and perform different biological functions. Similarly, microphase separation in hydrogels also brings interesting functions for hydrogels. For example, for some hydrogel containing polymers with a lower critical solution temperature (LCST), the polymers are well hydrated for temperature below LCST. Once the temperature is elevated above LCST, these well-hydrated polymers collapse, resulting in polymer rich and polymer poor domains. Another example is block polymers with some segment sequences are hydrophobic and some are hydrophilic. Microphase separation occurs spontaneously in these polymers to reduce the free energy of system when forming hydrogels. Depending on the type of microphase separation and the arrangement of phase structure, the hydrogels may have different functionalities, such as stimuli responsive, and structure color.

Crystallization in hydrogels involves the crystallization of polymer network itself and the crystallization of additives. One example is cellulose, which is one of the most used polymers that have ability to crystallization in hydrogels. Celluloses have strong intra and intermolecular hydrogen bonds, which cause nanoscale crystallization regions with highly ordered chains and amorphous regions with disordered chains. The nanocrystals act as multifunctional crosslinkers and reinforcing fillers to improve the mechanical performance of the hydrogels. Another example is colloidal crystals. A crystalline colloidal array has been polymerized into a hydrogel, with a lattice spacing matches the wavelength of visible light. The gel network swells in the presence of some analytes that can bind to polymer network, due to the increased osmotic pressure. The gel changes color by swelling, which can be used as intelligent chemical sensing materials. The third interesting example is the increased bonding of tough hydrogels to bone by adding hydroxypatite (HAp) nanocrystals into a double network gel. Bonding between tough hydrogel and bone is challenging and impedes the application of hydrogels in biological applications. A recent work by Nonoyama et al. shows that by mineralizing calcium-phosphate-hydroxide salt HAp nanosphere crystals into the surface layer of a DN gel, the gel spontaneously bonds to defected bones robustly in vivo.

Hydrogels with inorganic additives represent an emerging class of materials with robust functionalities, as many inorganic additives themselves are highly functional. Diverse inorganic additives have been incorporated into hydrogels, such as nanoparticles, clays, and titinate nanosheet. The functionalities bring to hydrogels by inorganic additives include controllable drug release, electron conduction, stimuli response, mechanical enhancement, and so on. For example, carbon nanotubes are widely used to fabricate hydrogel composite due to their unique properties, such as electrical conductivity, high mechanical strength, and low mass density. By incorporating 3 wt% of carbon nanotubes into hydrogels leads to an increase of 358% in electrical conductivity and an increase of 80% in toughness at the same time. Another example is that, by embedding negatively charged unilamellar titinate nanosheets with a quasicrystalline structural ordering into a polymer network, the resultant hydrogel shows anisotropic optical and mechanical performance.

MULTIPLE FUNCTIONALITIES OF A HYDROGEL WITH AGGREGATED STRUCTURE

Here, we give an example to show that incorporating an aggregated structure into a simple hydrogel can achieve multiple functionalities at the same time. Polycrylamide (PAAm) hydrogel itself has poor functionality. Haque et al. incorporated membrane-like poly(dodecylglyeryl itaconate) (PDGI) bilayers in lamellar structure with unidirectional alignment into a PAAm hydrogel by applying shear flow in the precursor solution. This gel, named as PDGI/PAAm hydrogel, exhibits multiple functionalities, such as 1D swelling, anisotropic modulus, stress/strain tunable structural color, 1D diffusion for small molecules, and so on (Figure 2). Dodecylglyeryl itaconate (DGI) is a lipid molecule that can self-assemble into lamellar liquid crystals in water. By imposing a strong shear flow to a precursor solution containing acrylamide, DGI, initiator, and crosslinker between two glass plates and then conducting polymerization, macroscopic single-domain PDGI bilayers are intercalated between PAAm hydrogel layers, resulting in a plate-like PDGI/PAAm hydrogel with lamellar structure consisting of an alternatively stacked bilayer/hydrogel layer with unidirectional alignment.

The elastic modulus of PDGI bilayers is several MPa, while PAAm network only has a modulus of several kPa. The large difference in elastic modulus of a PDGI bilayer and a PAAm hydrogel layer results in an anisotropic mechanical property of PDGI/PAAm gel in the directions parallel and perpendicular to the lamellar layers. The elastic modulus in the direction parallel to the lamellar layers is contributed by the sum of PDGI and PAAm layers, while the modulus in direction perpendicular to the lamellar bilayers is mainly from PAAm layer. Thus, the elastic modulus in these two directions has 10 times difference. Swelling of polymer network is known as cooperative diffusion and usually isotropic. In contrast, the PDGI/PAAm gel sheet does not swell in the length and width directions, while it significantly swells in the thickness direction. The unidirectional alignment of rigid and water-impermeable PDGI bilayer completely restricted the in-plane swelling of the PAAm hydrogel layers, which enhances the out-plane swelling of the hydrogel layer. The diffusion of small hydrophilic molecules penetrating through the hydrophobic PDGI layers is difficult, thus, PDGI/PAAm gel can also be used for direction-controlled diffusion for hydrophilic molecules.

The unidirectional alignment of lamellar structure endows the gel bright structural color. The periodic distance of the lamellar bilayers is several hundreds of nanometers, fulfilling the Bragg’s law of diffraction of visible light. The color of PDGI/PAAm gel can be tuned by changing the DGI concentration in precursor solution. The color is sensitive to the mechanical stimulation perpendicular to the lamellar direction. When applying compressive stress/strain to the gel, the gel color exhibits blue shift. This change is reversible, and the color recovers to initial state after removing the stress/strain. However, the recovery time is relatively long.
FIGURE 2 Multiple functionalities of a PDGI/PAAm lamellar hydrogel. PAAm gel has poor functionality. By embedding thousands of PDGI bilayers stacked unidirectionally into a PAAm hydrogel, the resulting gel (PDGI/PAAm gel) has robust functionalities, such as structural color, stress/strain response, 1D swelling, anisotropic molecular diffusion, anisotropic modulus, self-recovery, high mechanical strength, and high toughness. Reproduced with permission from the literatures [11,47–50].

(longer than 10 min), due to the strong viscoelasticity of the well-packed PDGI bilayer. Later, Yue et al. conducted a postmodification hydrolysis reaction on PDGI/PAAm hydrogel by converting some amide groups in PAAm gel into carboxyl groups to provide sodium polyacrylate.[47,54] The partially hydrolyzed PAAm layers carry charges, which exert high osmotic pressure to split the large PDGI bilayers into small domains. The resulting gel has an ultrafast responsive time of about 0.1 ms to mechanical stimulation, with a high spatial resolution and excellent mechanical stability. The PDGI/PAAm can also have thermal and pH responsive behaviors by introducing a thermal and pH responsive poly(acrylic acid) network interpenetrated with the PAAm network.[55]

The bilayers not only diffract visible light to give structure color of the gel, but also enhance the mechanical strength and toughness.[48] Both the fracture stress and fracture strain of PDGI/PAAm gel are dramatically larger than the PAAm gel under tensile deformation. PDGI/PAAm gel exhibits a clear yielding, arising from the dissociation of PDGI lamellar bilayers with strong hydrophobic interaction. The dissociation of hydrophobically aggregated PDGI bilayers under deformation dissipates a lot of energy and gives a large hysteresis in loading-unloading curve, endowing the gel a high toughness. As the dissociation and association of hydrophobically aggregated PDGI is reversible, PDGI/PAAm gel shows self-recovery behavior. The bilayer structure also gives the gel crack resistance by forming huge blunting. When a PDGI/PAAm gel with a crack is stretched, a huge blunting occurs at the crack tip, and there is no stress concentration in front of the crack tip. In contrast, the crack propagates easily in the PAAm gel even at small deformation. A recent study suggests that structure transformation from lamellar bilayers to hierarchical fibrous structures of PDGI layer is crucial to the crack resistance of PDGI/PAAm hydrogels.[56]

STRUCTURAL COLOR

Structural color widely exists in living organisms, such as chameleons, tropical fishes, peacocks, and beetles (Figure 3A). The structural color origins from the diffraction of light on the periodic nanostructure. As mentioned above, PDGI/PAAm gel shows bright structural color due to its periodic bilayer lamellar structure. In addition to the PDGI/PAAm gel, many other hydrogels also show structural colors by various kinds of aggregated structures.[40,54,55,61–63] In this section, we will discuss this topic in more detail considering its vital importance. The materials with periodic nanostructure and structural color are usually named as photonic crystals. Such materials have promising applications in display, optical communication, thermal sensing, electric and magnetic devices, and so on.[62,64] Hydrogels with photonic structure have many advantages compared with other photonic materials. Hydrogels are high stretchable and can undergo reversible volume change by a wide range of external stimuli, such as light, temperature, and pH.[44] At the same time, they are soft and wet, and usually biocompatible. These features enable photonic hydrogels to offer technological advances in many fields, especially in intelligent skins, wearable electronics, and biological sensors[65–69].
Block copolymer is a fascinating material platform for fabricating photonic gels. Block copolymer composed of two or more incompatible blocks spontaneously undergo microphase separation to reduce free energy of the system. Depending on the polymer type, molecular weight, and the interaction parameter, different aggregated structures could be formed to fabricate photonic gels, such as lamellae, cylinder, gyroid, and sphere. For example, Lim et al. used a diblock copolymer composed of hydrophobic block-hydrophilic polyelectrolyte block, polystyrene-b-poly(2-vinyl pyridine) (PS-b-P2VP), to construct photonic hydrogels (Figure 3B). This diblock copolymer forms a lamellar structure with a nonswollen PS layer and a swollen P2VP layer arranged alternatively. The swelling of P2VP layers can be tuned by changing counterions, as the solubility of P2VP in aqueous solution depending on the hydration nature of the counterions. By selecting proper counterions, a full-color tunability from blue to red can be realized.

Another material platform for fabricating photonic gels is colloidal crystals. By incorporating periodically packed colloidal particles into a gel matrix or forming a porous gel matrix by etching away the precursor colloidal particles, the obtained gels exhibit structural color. For example, Weissman et al. created phonic gel by embedding colloidal crystals of polystyrene spheres within a poly(N-isopropylacrylamide) (PNIPAAm) network. PNIPAAm network has a temperature-induced volume phase transition, which swells and contracts with temperature, varying the crystalline array. Thus, the structural color of the gel can be thermally tunable across the entire visible spectrum. Takeoka et al. created a periodically ordered interconnecting porous structure in the gel by using a silica colloidal crystal as a template. They first embedded silica colloidal crystal into a PNIPAAm gel, and then dissolved the silica colloidal crystal by hydrogen fluoride aqueous solution. The gel with periodic porous shows structural color, and the structural color can be simply tuned by changing the temperature or crosslinker concentration during polymerization.

The above structural hydrogels we discussed are based on simple periodic structure, and the structural color depends on the observation angle. That means the structural color changes when changing the observation angle. The angle-dependence of structural color may limit the application of these hydrogels in some fields, such as displays with wide observation angles. Efforts have been made to develop the hydrogels with angle-independent structural color. For example, Zhang et al. spread pollen particles with spikes into the colloidal crystal arrays before the molecular self-assembling process (Figure 3C). The colloidal self-assemblies into small crystal domains with different
FIGURE 4  Rapid thermoresponsive behavior of hydrogels with aggregated structures. (A–C) Thermoresponsive behavior of PNIPAAm/TiNSs hydrogel and its design as an actuator. (A) Structure of the PNIPAAm/TiNSs hydrogel and the deformation of a hydrogel rod in a glass capillary on rapid heating (i) and cooling (ii) between 15 and 50 °C. (B) Structure design of an L-shaped symmetric PNIPAAm/TiNSs hydrogel actuator and its mechanism. (C) The moving distance profiles of the actuator on a flat, horizontal base with alternate heating and cooling between 25 and 45 °C at a rate of 0.1 °C s⁻¹. (D–F) Thermoresponsive behavior of a PAAc/CaAc hydrogel. (D) Mechanism of fast thermal hardening of a PAAc/CaAc hydrogel. (E) The gel without microphase separation at 25 °C is transparent and soft (i) and cannot support a 10 kg weight (ii). (F) The gel instantly becomes opaque and rigid when heated to 60 °C (i) and can support the weight (ii). Reproduced with permission from the literatures [25,84]

orientations. These domains reflect the light to a wide range of viewing angles, endowing the gel an angle-independent structural color. The angle-independent structural color can also be realized in PDGI/PAAm gels (Figure 3D). Plate-like PDGI/PAAm gels show strong angle-dependent structural color. Haque et al. changed the bulk and internal geometries of PDGI/PAAm gels by shearing and polymerizing the precursor solution in a tube. [60] The gel obtained in this way has a rod shape, and the bilayer lamellar structure is coaxially aligned in a cylindrical geometry. As a result, this rod-like gel exhibits an angle-independent color.

RAPID THERMAL RESPONSE

Hydrogels are known as their ability to reversible change the volume under a wide range of stimuli, such as temperature, pH, light, and ionic strength.[11] For the conventional gels, the volume phase transition takes a long time, typically in the order of hours for a gel with a 1 mm size.[85,86] This is because the volume phase transition of hydrogels happens by taking in or squeezing out of water molecules, and the water molecules need to travel by a length scale of the sample size through the mesh size of polymer network.[53] Thermal responsive hydrogels are a type of hydrogels that undergo a large volume change at a critical temperature, accompanying with a coil–globule transition in chain conformation.[87] Here, we take thermal responsive hydrogels as an example to show that, in the presence of aggregated structure, the responsive time of the phase transition can be shortened to the order of seconds, and the volume of the gel keeps almost the constant during phase transition.

Aida et al. prepared a PNIPAAm hydrogels containing layered structure with cofacially oriented unilamellar electrolyte titanate(IV) nanosheets (TiNSs, Figure 4A).[20,84] The thermal responsive behavior of this gel is significantly different from the conventional PNIPAAm-based hydrogel. The conventional PNIPAAm-based hydrogel shrinks and swells in volume on heating and cooling, respectively, accompanying with a long responsive time. For the rod-like PNIPAAm gel containing cofacial TiNSs, it lengthens and shortens upon heating and cooling, respectively, because of the expansion and contraction of the cofacial TiNS distance (Figure 4A). This thermal responsive behavior happens with a very short responsive time (in the order of seconds with ~ 1 mm size) and without substantial volume change. Benefiting from these advantages, Aida et al. designed a bipedal walking actuator made of an L-shaped hydrogel with an oblique nanosheet configuration (Figures 4B, C). When placing its forefoot and backfoot on a flat base, the actuator walks unidirectionally upon heating and cooling cycling, without requiring any external physical bias. Later, Yamamoto et al. built a theory to explain this unique thermal responsive behavior.[88] The main idea of this theory is that the nanosheets constrain the
deformation of polymers between them, while other polymers deform relatively freely. During thermal response, the solvent flow between the constrained region and the unconstrained region happens, instead of flow out of the gel. Therefore, the solvent molecules only travel with a length scale of nanosheet, giving a short responsive time and anisotropic deformation.

Nonoyama et al. reported a fast thermal switching from soft to hard without volume change in a weak polyelectrolyte poly(acrylic acid) (PAAc) hydrogels containing calcium acetate (CaAc). The carboxyl side groups of PAAc form dynamic ionic interaction with acetate ions and Ca$^{2+}$. The hydrophobic acetate moieties dehydrate at a critical temperature. The dehydration strengthens the ionic interaction, because the Coulombic interaction is inversely proportional to the permittivity of the environment surrounding the ionic bonds. Such an interplay between hydrophobic and ionic interaction results in a strong spinodal decomposition of the hydrogel into a polymer dense phase and a polymer sparse phase (Figure 4D). The dehydration of the dense phase brings about a rubbery-to-glassy transition, which rapidly freezes the mobility of polymer chains and confines the water in pores to show microsyneresis. As the characteristic phase size is from about 100 nm to 1 μm, the time for water molecules travel along the phase size is very short. Consequently, the gel exhibits rapid thermal switching and unique thermal hardening without macroscopic volume change (Figures 4E, F). By raising temperature from 25 to 70°C, increases of 1800-, 80-, and 20-folds, in stiffness, strength, and toughness were observed, respectively.

HIGH MECHANICAL PERFORMANCE

Mechanical performance is crucial for the application of hydrogels. Conventional hydrogels are mechanically soft and weak, due to the lack of mechanical dissipation. The authors’ group invented double network hydrogels that are strong and tough in 2003 and addressed the mechanical weakness of hydrogels. The basic idea to make hydrogels tough is to introduce sacrificial structure into hydrogels. The sacrificial structure breaks preferentially during deformation, dissipating substantial amount of energy and giving a high toughness of the hydrogel. Inspired by the double network hydrogels, various aggregated structures have been used as sacrificial structures to toughen hydrogels. For example, Sun et al. developed a hydrogel composed of a physical network and a chemical network. The polymer chains in physical network associate through metal–ion interaction. This association reversibly breaks and reforms during deformation to dissipate energy. This gel containing 90% of water has a fracture energy of 9000 J/m$^2$ and can be stretched beyond 20 times of the initial length. This gel is also crack insensitive. The gel with a notch can be stretched about 17 times of the initial length.

Some aggregated structures can also endow hydrogels extra high stiffness and stretchability. For example, Mredha et al. reported a type of anisotropic hydrogels with well-aligned multiscale fibrous structure from nanoscale to microscale. These hydrogels were obtained by confined drying of a dilute physical hydrogel with relatively rigid polymers, such as cellulose and alginate, in air and then reswell in water. During drying process, the polymer chain orients along the confined direction and the polymers form nanofibrils through supramolecular interaction. The nanofibrils further form thick fibers, leading to a hierarchical fibrous structure of the gels (Figure 5A). These gels possess Young’s modulus from tens to hundreds of MPa and fracture stress of tens of MPa, which are comparable to the natural ligaments. Jeon et al. prepared a hydrogel system with hierarchical interactions, including hydrophobic association, multiple hydrogen bonds, and encapsulation (Figure 5B). These hierarchical interactions allow the hydrogels to sustain a deformation up to 100 times of the original sample length, and the gel can completely self-heal within 30 s after cutting.

A recent study shows that the fatigue resistance can be greatly enhanced by the aggregated structure. The fatigue resistance of hydrogels, characterized by the fatigue threshold above which the crack starts to propagate under cyclic loading, is reported in the same order as their intrinsic fracture energy. Lin et al. found that incorporating the nanocrystals in a polyvinyl alcohol hydrogel substantially enhances the fatigue threshold. This is because in amorphous hydrogels, the fatigue thresholds are the energy per unit area to fracture one layer or several layers of polymer chains. While in hydrogels containing crystals, the fatigue thresholds are the energy per unit area required to fracture crystalline domains. The fatigue threshold of PVA gel increases with increasing the crystallinity and exceeds 1000 J/m$^2$ when the crystallinity of gel is 18.9 wt%. While the gel with high crystallinity has a high modulus and low water content. Later, Lin et al. used a mechanical training method to induce the alignment of the nanofibrils with nanocrystalline domains and obtained a gel with high fatigue threshold, high water content, and low modulus at the same time. The crystallinity of this gel is only 2–3 wt%, and the high fatigue resistance comes from the crack pinning by the aligned nanofibrils (Figure 5C).

The combination of multiple mechanical properties, including stiffness, strength, toughness, fatigue resistance, and self-healing, is also possible in a hydrogel with aggregated structure. For example, Sun et al. developed a class of hydrogels composed of polyampholytes (PA) that bearing randomly dispersed cationic and anionic repeat groups. PA hydrogels have a multiscale structure: reversible ionic bonds between opposite charges at ~0.1 nm scale, transient polymer network at ~1 nm scale, permanent polymer network at ~10 nm scale, and bicontinuous hard/soft phase networks at ~100 nm scale. Such a multiscale structure allows the gel a multiple mechanical performance: high stiffness (Young’s modulus: 0.1–1 MPa), high toughness (fracture energy: 1000–4000 J/m$^2$), 100% self-recovery, and high fatigue resistance. During deformation, the bicontinuous phase network shows affine deformation up to a large strain and then an extensive nonaffine deformation. During affine deformation, the nanoscale chain conformation changes and the ionic bonds break to dissipate energy. During nonaffine deformation, the hard phase network ruptures, while the soft phase network takes over the stress and reduces stress concentration, allowing more rupture of hard phase to dissipate energy. This multiscale rupture process dissipates a significant amount of energy and gives the high toughness of PA gels. Recently, Li et al. found that the high fatigue resistance of PA gel is associated with the phase-separated
FIGURE 5  High mechanical performance of hydrogels with aggregated structures. (A) Ultra stiff hydrogel with well-aligned multiscale fibrous structure. Scanning electron images to show the uniaxially aligned microfibers in the surface (a-i to a-v) and axial cross-section of the gel (a-vi and a-vii). Each microfiber consists of a bundle of several submicrometer-sized fibers (a-ii), as illustrated in (a-iii). Each submicrometer fiber was further composed of a nanofibrillar array (a-iv), as illustrated in (a-v). (B) Ultra stretchability of hydrogels with hierarchical interactions, including hydrophobic association, multiple hydrogen bonds, and encapsulation. (i) Schematic to show the structure of this gel. A gel specimen (ii-iii) before and (iv) after stretching. (C) High fatigue resistance of a hydrogel with different alignments of nanofibrils: (i) the longitudinal direction of nanofibrils is perpendicular to the notch direction; (ii) the longitudinal direction of nanofibrils is parallel to the notch direction; (iii) the nanofibrils have no preferred orientation. Reproduced with permission from the literatures[23,28,89].

structure.\[^{109}\] In cyclic loading, the bicontinuous phase network orients along the stretching direction, resulting in a pronounced crack blunting and crack deceleration effect, which gives an extremely slow crack growth even above the fatigue threshold of PA gel.

### DYNAMIC MEMORIZING-FORGOTTING BEHAVIOR

The aggregated structures we discussed above are in equilibrium or quasi-equilibrium state. In biological tissues, many functions are executed with structures stay in a nonequilibrium and dynamic state.\[^{111-113}\] Introducing nonequilibrium aggregated structures into hydrogels is challenging. A very recent work by Yu et al. shows that the hydrogel with a nonequilibrium structure has dynamic memorizing-forgetting behavior, in analogy to human brain (Figure 6).\[^{110}\] This work shows that the hydrogels containing dynamic bonds can be encoded with a two-dimensional (2D) information through thermal learning, and the encoded information spontaneously forgets with time. The forgetting time is proportional to the learning time or learning strength.

This dynamic memorizing-forgetting behavior of hydrogels is based on the asymmetric swelling and shrinking kinetics caused by the formation of transient aggregated structure. Hydrogels containing physical bonds swell by absorbing water upon heating (Figure 6A). Because at high temperature, the number of associated physical bonds increases, which increases the osmotic pressure of the gel. By a sudden cooling, the number of associated physical bonds increases quickly, while the adsorbed water at high temperature cannot be expelled out of gel instantly, due to slower water diffusion than the heat conduction. Consequently, the water molecules are trapped between the aggregated polymer chains and form a transient frustrated structure, resulting in a slow shrinking process. The swelling upon heating can be considered as a thermal learning, while shrinking after cooling can be considered as a forgetting. The asymmetric swelling and shrinking kinetics allows the gel a fast learning, while a slow forgetting. Moreover, the formation of transient frustrated structure causes a transparency change of the gel, which can be utilized to retrieve the memorizing information.

As shown in Figures 6B and C, through a spatially controlled thermal learning process, a PA gel can memorize various information, such as a word “GEL,” a pattern of

| Hydrogel          | Young's modulus, [MPa] | Fracture stress, [MPa] | Fracture strain, [%] | Water content, [wt%] |
|-------------------|------------------------|------------------------|----------------------|----------------------|
| Alginate          | 203–367                | 20–22                  | 51–201               | 56–57                |
| Cellulose         | 59–342                 | 25–53                  | 35–267               | 58                   |
| Knee ligaments    | 65–447                 | 13–46                  | 11–44                | 60–70                |
“umbrella,” a “fish,” and a “twig.” The memorized information is highly stretchable, benefiting from the high stretchability of the gel. The memorized information gradually forgets with time, without any external stimuli (Figure 6D). The forgetting time increases with learning time and learning temperature, until the gel reaches swelling equilibrium during learning. Sequential forgetting process can also be realized through programming the thermal learning time or leaning temperature. This work is the first example to realize dynamic memorizing-forgetting behavior in network materials. Although this work is still in its infancy, and the memory behavior in hydrogels does not have memory plasticity like that in human brain, it will inspire further research on developing life-like materials based on the nonequilibrium structure of soft matter.

CONCLUSION AND REMARKS

Functional hydrogels are desirable in diverse applications. Inspired by nature, various functional hydrogels have been developed in recent years by implementing aggregated structures into hydrogels. Different aggregated structures impart very different functionalities of the hydrogels. Here, we
reviewed the strategies used to construct aggregated structures and discussed the relationship between the aggregated structure and the functionalities of the hydrogels. The aggregated structures can be formed by molecular self-assembling, microphase separation, and crystallization of gel network itself or the additives. A simple aggregated structure can bring robust functionalities and a combination of multiple mechanical performances at the same time. Moreover, incorporating a nonequilibrium aggregated structure in hydrogel can construct dynamic memorizing-forgetting behavior in hydrogels.

Compared with the sophisticated structure in biotissues, the aggregated structure developed in hydrogels is still too simple, and thus their functionalities are very limited. Creating hydrogels with elaborate structure from nano to macroscale and thus elegant functionalities will be the next opportunity for material scientists. The precisely control of aggregated structure in hydrogels is rather challenging. Although different strategies like molecular self-assembling, microphase separation, crystallization, and additives have been used to form aggregated structure in hydrogels, these structures are limited to one or two specific length scales. To realize the precise control of aggregated structure in different length scales from nano to macroscale, a combination of multiple strategies, together with the precisely control of external filed, such as stress, flow, or/and electric field, may be required. Furthermore, well-defined polymers or molecules are also the key for constructing elaborate structure in hydrogels.

Another large difference between the biotissues and hydrogels is that the structures in biotissues are formed via a nonequilibrium and dynamic process, while the aggregated structures in hydrogels are usually in equilibrium or near-equilibrium state. Research of hydrogels with nonequilibrium aggregated structure is starting now. As shown in Section 7, frustrated structure formed in hydrogels containing abundance of physical bonds upon cooling, enabling the hydrogel a dynamic memorizing-forgetting behavior. Although the dynamic memorizing-forgetting behavior of hydrogels is still far from the memorizing-forgetting behavior in human brain, this work points out further direction for developing life-like materials by utilizing soft matter with nonequilibrium structure. Recent effort on nonequilibrium chemistry also gives an inspiration on developing hydrogels with nonequilibrium structure. A recent work by Matsuda et al. shows that by mechanical training, a double network gel can self-growth and self-strength by mechanochemical transduction (Figure 7). The polymer chains break and generate mechanoradical under repetitive mechanical stress, initiating the polymerization of the monomers supplied from the outer environment, in analogy to the metabolic process of growth and remodel of muscle in human body. As the mechanochemical transduction can be applied to different chemical species, this strategy is promising in developing hydrogels with on-demand structure and functionality.

ACKNOWLEDGMENTS
This research was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Nos. JP17H06144 and JP19K23617) and the Institute for Chemical Reaction Design and Discovery (ICReDD) established by World Premier International Research Initiative (WPI), MEXT, Japan.

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How to cite this article: Cui K, Gong JP. Aggregated structures and their functionalities in hydrogels. Aggregate. 2021;2:e33. https://doi.org/10.1002/agt2.33