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Fabrication of Bioinspired Hydrogels: Challenges and Opportunities

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ABSTRACT: Since the birth of synthetic hydrogel sixty years ago, hydrogels possessing various useful properties and functions have been developed. The research directions of hydrogels have expanded to diverse application fields as well. However, in contrast to natural hydrogels found in biological soft tissues, which have elaborate structures from molecular to macroscopic scales and sophisticated functions, synthetic hydrogels only have very simple structures and naive functions. We have great opportunities to develop hydrogel materials through learning from nature. This

perspective discusses the opportunities and challenges in the fabrication of hydrogels with excellent physical functions by mimicking biological structures at different length scales.

1. INTRODUCTION:

This is the year of the 100th anniversary of Hermann Staudinger proposing the macromolecular theory. In the field of hydrogels, it is also the 60th anniversary of the birth of synthetic hydrogels.

In 1960, Wichterle and Lim synthesized the first hydrogel by copolymerization of 2-hydroxyethyl methacrylate with ethylene glycol dimethacrylate.¹ Since then, hydrogels have drawn research interest owing to their unique integration of solid and liquid properties.

Especially in the past two decades, research on hydrogels has progressed rapidly. The research directions have expanded from the initial interest in fundamental science to diverse application fields, including water treatment, artificial organs, wearable electronic devices, and soft machines.²⁻⁷ Nowadays, hydrogel has become one of the most extensively studied materials in interdisciplinary research fields.

Hydrogel, in general, is defined as a three-dimensional polymer network containing a large amount of water. A typical hydrogel can be simply fabricated by crosslinking hydrophilic polymer chains or polymerization of water-soluble monomers with crosslinkers.⁸ In the beginning, research on hydrogels was focused on such relatively simple chemically crosslinked polymeric networks for studying their fundamental characteristics such as swelling/deswelling

kinetics and equilibrium,^{9, 10} solute diffusion,¹¹ volume phase transition,¹²⁻¹⁴ sliding friction,^{15, 16} as well as for studying applications such as in ophthalmology and drug delivery.^{17, 18} With the continuous advancements in hydrogel research, its focus shifted from simple networks to “responsive” networks. At this stage, various kinds of hydrogels capable of responding to changes in environmental conditions such as pH,¹⁹ temperature,^{20, 21} electric^{22, 23} and magnetic fields,^{24, 25} etc., have been developed. Hydrogel actuators responding to electric and magnetic fields were proposed.^{22, 26} However, the hydrogels of the time were usually either too soft or too brittle mechanically, which extremely limited their potential applications. With the new millennium, hydrogels have also entered a new era with groundbreaking enhancements of their mechanical properties.²⁷⁻³⁰ This success resulted in many interdisciplinary studies of hydrogels. Nowadays, hydrogels stronger and tougher than muscles and cartilages can be made by various chemistries with energy dissipative structures.^{27, 31-38} Moreover, other functions, like self-healing,³⁹⁻⁴¹ multiple stimuli-response,⁴²⁻⁴⁸ adhesion,^{37, 49-51} superwettability,^{52, 53} etc., have also been achieved. The innovative development of strong and tough hydrogels has greatly expanded potential applications of this material in various fields, including soft machines, artificial organs, regenerative medicine, etc.^{5, 33, 54-57}

However, compared with natural hydrogels seen in biological soft tissues, synthetic hydrogels are still simple in structure and naive in function. After hundreds of millions of years of evolution, biological soft tissues achieved structures with two characteristics. One is their water-containing structure. Most soft tissues contain 50-85% of water by weight. The hydroscopic structure enables

biological soft tissues to serve as a medium for dynamic biological processes. The other is their elaborate structure, featuring multi-components, order-disorder, and hierarchy ranging from the molecular to macroscopic scale. The fact that biological soft tissues contain a suitable amount of water to ensure molecular mobility and, at the same time, they have elaborate structures is their key quality that enables biological tissues to have sophisticated functions. In contrast, synthetic hydrogels usually have an amorphous and isotropic structure. Therefore, there are great opportunities in development of innovative synthetic hydrogels with superb functions by inducing super-structures analogous to those present in natural hydrogels. In recent years, many efforts have been made towards developing various kinds of bioinspired hydrogels. In this perspective, we intend to discuss the challenges and opportunities for the fabrication of new hydrogels by mimicking biological structures at different length scales, using examples learned from nature reported in recent years (Figure 1). We will mainly focus on, but will not limit to, the hydrogels that show excellent physical functions.

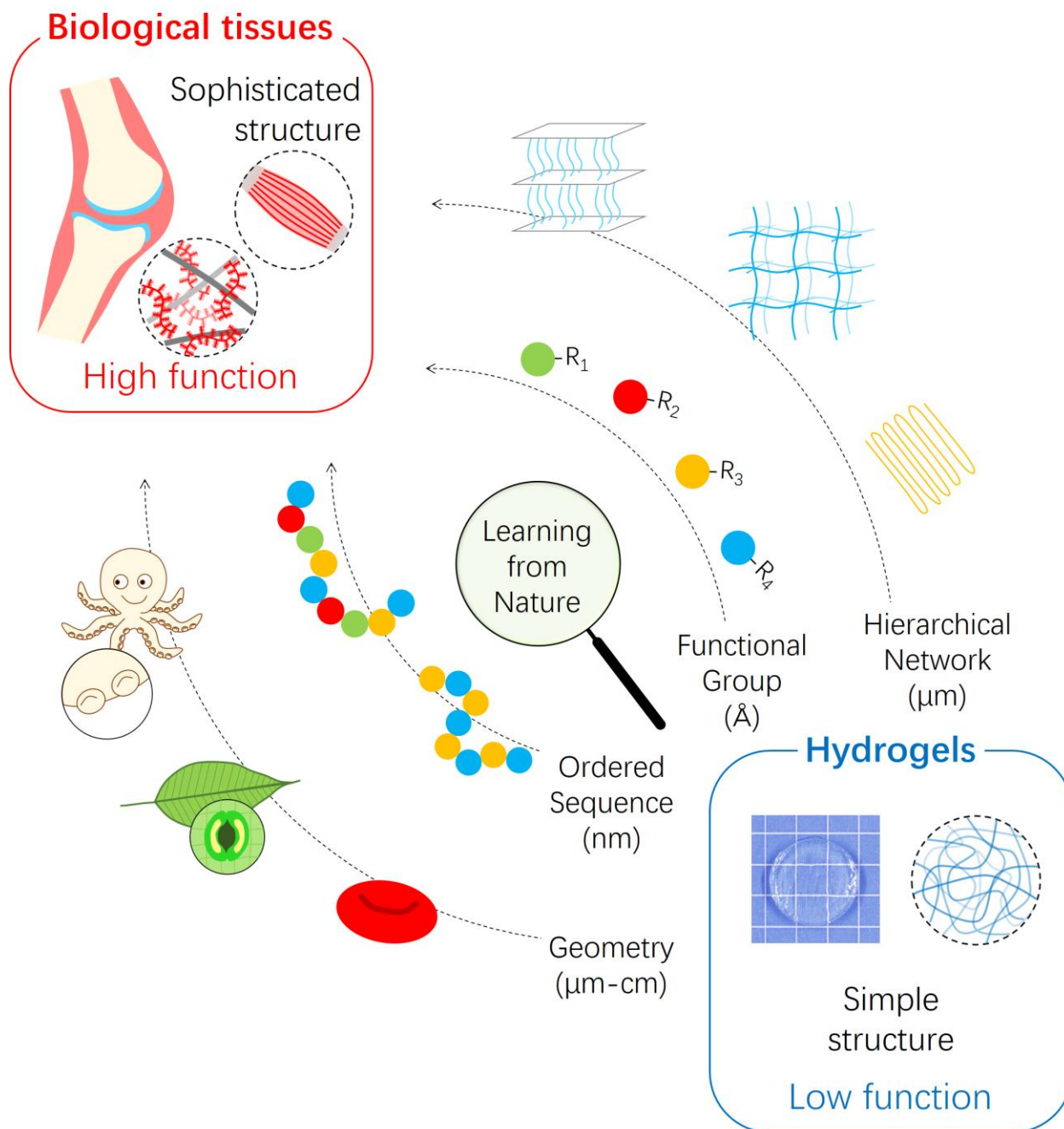


Figure 1. Challenges and opportunities in the fabrication of bioinspired hydrogels at different length-scales and their physical functions. At the molecular level, designing monomers with specific functions to mimic biomolecules like amino acids. At the nanometer scale, controlling the monomer sequence of synthetic polymers imitating biomacromolecules. At the sub to

micrometer scale, controlling network topological structure and self-assembly structure by intermolecular interaction, as in DNA or protein folding. At the macroscopic level, designing functional geometry or morphologies, inspired by biological systems.

2. MULTISCALE LEARNING

2.1 Building blocks. The basic building block of polymeric materials is the monomer. In biosystems, the main basic units are amino acids, nucleotides, and monosaccharide, which constitute protein, DNA, and polysaccharide, respectively. In the synthetic field, thanks to the development of organic chemistry, numerous monomers are available. The types of monomers are much more numerous than the natural building blocks. Mimicking nature even at the monomer level, at the lowest length scale, can impart certain specific functions to hydrogel materials.

One of the most successful examples is the underwater adhesion, which is challenging for synthetic adhesives but is achieved by sessile marine organisms like mussels. It has been found that L-3,4-dihydroxyphenylalanine (DOPA) is the key component in adhesive proteins for underwater adhesion. Subsequently, mussel inspired catechol chemistry has become a research hotspot in the past decade, especially in hydrogel field. Catechol is capable of diverse chemistries. It forms hydrogen bonds through -OH groups, π - π interactions with another aromatic groups, cation- π interactions with positively charged groups or cations, coordinate

bonds with metal ions or metal oxide surfaces. It can also be oxidized into highly reactive forms to react with itself or nucleophiles (i.e. -NH_2 , -SH) forming covalent bonds.^{58, 59} In the context of catechol use as a hydrogel building block, research has been performed on modifying a polymerizable group on catechol or introducing catechol onto polymer chains.⁶⁰⁻⁶⁴ In the early studies, the catechol group was used as a chemical crosslinker in the network by self-polymerization in the presence of an oxidizing reagent.⁶⁵ In 2011, inspired by the pH jump experienced by proteins during maturation of a mussel byssus secretion, Holten-Andersen et al. developed a simple method to control catechol- Fe^{3+} interpolymer cross-linking via pH adjustment, which yields a self-healing hydrogel (Figure 2a).⁶⁶ After this pioneering work, the mussel-inspired catechol group and its derivatives (e.g. pyrogallol and tannic acid) became the new favorite crosslinkers in the hydrogel field. The diverse chemistries of catechol group (or its derivatives) endow the hydrogel with various functions and properties, including self-healing,⁶⁷ mechanical tunability,⁶⁸⁻⁷⁰ adhesion,⁷¹⁻⁷³ stimuli responsiveness,⁷⁴⁻⁷⁶ and free radical scavenging ability.^{77, 78}

The original intention of using catechol was to achieve underwater adhesion, as it has successfully been realized in the systems of elastomers,⁷⁹ glues,⁸⁰⁻⁸⁵ and polymer films/coatings.^{86, 87} However, to our knowledge, underwater adhesion has not been realized using hydrogels. The free catechol group is the key for adhesion; yet, in hydrogels, it is usually either occupied by metal ions or oxidized into quinone (or both), losing its adhesion ability.^{73, 88} Furthermore, the hydrophilic feature of hydrogel makes it hard to remove the hydration layer

from the surface, which is the key step for underwater adhesion. By learning from mussels, scientists have realized that simply using catechol groups is insufficient for underwater adhesion.^{59, 89} More recent attempts to accomplish underwater adhesion of hydrogels include controlling the redox chemistry of catechol to prevent the oxidation, as well as introducing hydrophobic residues to polymer chains to break hydration layer.^{88, 90, 91}

Multiple electrostatic interactions also play important roles in biological activities. In general, mixing oppositely charged polyelectrolytes leads to phase separation. However, this drawback of macroscopic coacervate can be prevented by introducing high entanglement of polymer chains. Our group developed a series of novel polyampholyte (PA) hydrogels by simple copolymerization of oppositely charged monomers at high monomer concentration at the charge balance condition (Figure 2b).³⁸ The multiple ionic bonds in the network endow the polyampholyte hydrogel with mechanical properties like high toughness and viscoelasticity, as well as self-healing, self-recovery, and adhesion abilities.^{51, 92-94} Based on this concept, our group further developed polyion-complex (PIC) hydrogels, which were obtained from a concentrated solution of oppositely charged polyelectrolytes.⁹⁵ Since the ionic bonds only exist between interpolymer chains, PIC hydrogels are much tougher than PA hydrogels prepared using the same monomer composition, especially at low monomer concentrations.⁹⁶

The strength of ionic interaction strongly depends on the local environment. Nature uses the cooperative effects of hydrophobic interaction and ionic interaction to gain thermal stability, as seen in thermophile proteins. Recently, inspired by thermophile proteins, our group developed

novel materials that undergo ultra-rapid, isochoric, and reversible switching from soft hydrogels to rigid plastics at an elevated temperature by using poly(acrylic acid) gel containing calcium acetate (Figure 2c).⁹⁷ By enhancing the electrostatic interaction in hydrophobic media at high temperatures, the hydrogels undergo significant spinodal decomposition and subsequent rubbery-to-glassy transition when heated to an elevated temperature without volume change.

Besides the synthetic monomers, biomolecules (e.g., DNA, protein, peptide) can also be used as building blocks in hydrogels. The specific recognition of such biomolecules endows the hydrogels with special functions. For example, Willner group has reported a series of shape-memory acrylamide–DNA hydrogels that exhibit multiple stimuli-responsiveness by manipulating the helix type of DNA crosslinking units.⁹⁸⁻¹⁰⁰ Another feature of DNA is that its length can be manipulated by introducing a complementary strand. This feature was used to easily tune the volume of a DNA–cross-linked poly-acrylamide hydrogel, expanding it as much as 100 times (Figure 2d).¹⁰¹ Besides DNA, proteins are also an outstanding crosslinker in hydrogel network construction. Dooling and Tirrell incorporated the proteins on the poly(ethylene glycol) (PEG) chains and used the association of proteins to crosslink the network. They found that subtle changes in the sequence can lead to different coiled-coil bundles of proteins, resulting in diverse relaxation behavior of the hydrogel network and the relaxation time varying over 5 orders of magnitude.¹⁰²

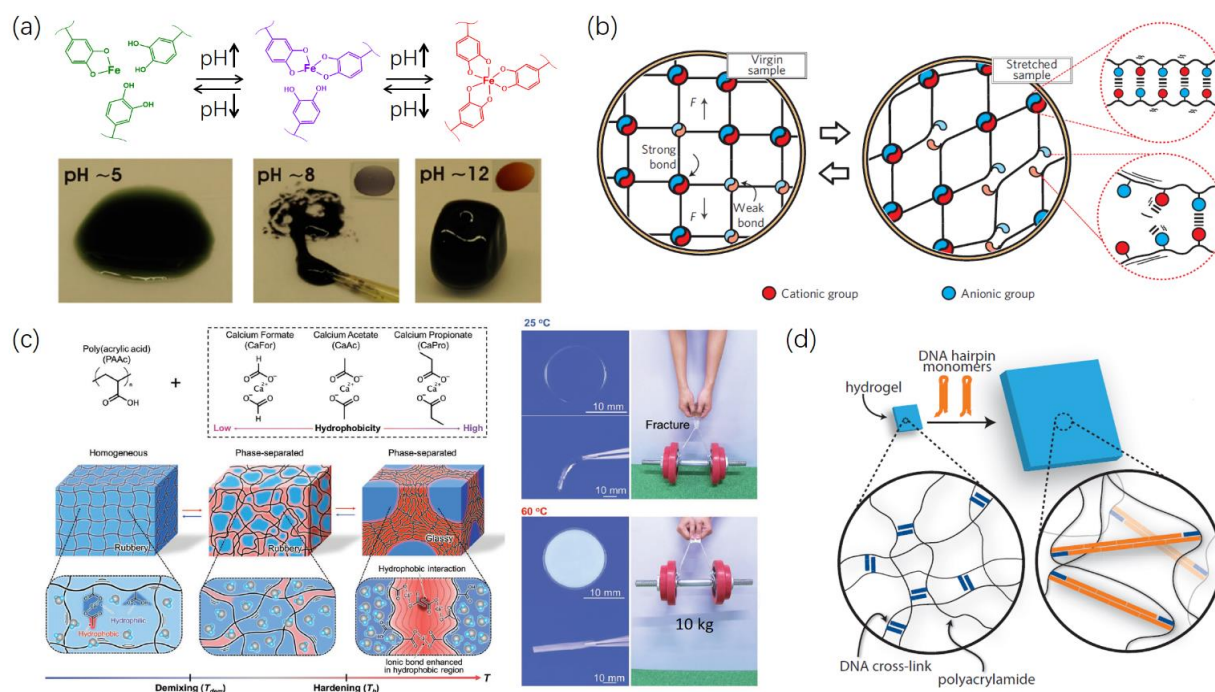


Figure 2. Functions through bioinspired monomer control. (a) Mussel-inspired catechol- Fe^{3+} coordination work as pH-sensitive crosslinks in the hydrogel. Reproduced with permission from ref⁶⁶. Copyright 2011 National Academy of Sciences. (b) Ionic bonds of different strengths in polyampholyte networks. The strong bonds serve as permanent crosslinking points, and the weak bonds act as reversible sacrificial bonds that rupture under deformation. Reproduced with permission from ref³⁸. Copyright 2013 Springer Nature. (c) Thermophile proteins inspired hydrogel that is thermally stiffened using cooperative effects of hydrophobic interaction and ionic interaction. Reproduced with permission from ref⁹⁷. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA. (d) DNA as a crosslinker for the fabrication of hydrogel with controlled swelling degree. Reproduced with permission from ref¹⁰¹. Copyright 2017 American Association for the Advancement of Science.

2.2 Polymers. Connecting monomers results in polymers. For polymers containing two or more types of monomers, the sequence of monomers dramatically influences the properties of a polymer. In a biosystem, biomacromolecules such as DNA and proteins have precisely controlled monomer sequences and molecular weights that enable them to fulfill well-defined functions. However, synthetic polymers have a much simpler structure; they are usually a homopolymer or a copolymer. Traditional methods, such as free radical polymerization, are useful for rapid synthesis on a large scale, but the monomer sequence and molecular weight distributions are poorly controlled. During the past decades, the field of polymer chemistry has developed greatly using diverse modern strategies, including solid-phase synthesis, click chemistry, step-growth polymerization, and reversible-deactivation radical polymerization (RDRP) techniques.¹⁰³⁻¹¹³ Nowadays, more and more well-defined polymers with controlled composition, monomer sequence, chain length, chain ends, and molecular weight distribution have been synthesized in the laboratory. However, the diversity of functional groups on these polymers is still limited, and the yields are generally measured in milligrams or up to a few grams, which limits their application in material science.¹⁰⁸ In the hydrogel field, the fabrication of novel functional hydrogels using desired polymers is still in its infancy. Especially, selecting specific monomers with a specific sequence when designing materials with specific functions is a big challenge.¹¹² The majority of polymers used for building a network are still homopolymers,¹¹⁴⁻¹¹⁶ random copolymers,^{38, 117} or polymer blends.^{31, 95} In recent years, the influence of monomer sequence on

the properties of hydrogels has gradually attracted the attention of researchers.¹¹⁸⁻¹²⁰

The approaches used to fabricate sequence-controlled polymer hydrogels can be divided into two categories. One uses biotechnology, which gives biomacromolecule-based hydrogels, and the other uses some unique polymerization methods, which gives synthetic polymer hydrogels. In the first category, the polymer chains are proteins or protein-based block copolymers that have well-defined sequences originating from these proteins.^{102, 120-127} In these hydrogels, the proteins self-assemble into either nanostructures or crosslinking domains, which enables the hydrogels to respond to pH, temperature, and ionic strength.^{121, 122} Kang et al. fabricated a series of peptide hydrogels with different multidomain peptide sequences and examined the effect of sequence on the morphology and expansion of encapsulated stem cells from human exfoliated deciduous teeth.¹²³ Their results suggested that the threonine-containing hydrogels are more selective, requiring the RGDS (R, arginine; G, glycine; D, aspartic acid; S, serine) sequence for cell attachment to occur, while the serine-based sequences are more proliferative and will support large increases in cell population even if bioactive sequences are not present. While synthetic biomacromolecules have precisely controlled monomer sequences and molecular weight, the limitations are also obvious, including low yields and high costs, low molecular weight, and lack of monomer structural diversity.¹⁰³

Compared with protein-based hydrogels using biotechnology, the studies on the fabrication and properties of synthetic hydrogels with controlled sequences are rare, as monomer sequences are difficult to control using conventional polymerization. But it is worth noting that this topic has

been studied in recent years.^{118, 119} For example, compared with a random sequence, the block-sequence of phospholipid polymers, which were obtained through two-step polymerization, needed much more gelation time owing to the different aggregate structures.¹²⁸ The study of poly(acrylamide derivative) hydrogels also showed that the monomer sequence type, random or blocky, has a strong impact on the swelling behavior of gels.¹²⁹ The randomly sequenced hydrogel property was an average of those of the two monomers, depending on monomer composition. On the other side, the block sequenced hydrogels behaved as if two components independently contributed to the swelling properties, which is probably due to the domain structure derived from two kinds of prepolymers. Washington et al. studied the impact of monomer sequence and stereochemistry on the swelling and erosion of biodegradable poly(lactic-co-glycolic acid) (PLGA) matrices.¹³⁰ By using segment assembly polymerization, they prepared a series of periodic copolymers and also random copolymers as a control. They found that the sequences have significant influence on the swelling and erosion behaviors of the polymers.

Very recently, our group fabricated a series of sequence controlled hydrogels that showed superior adhesion in seawater.⁹¹ We discovered that copolymers with adjacent cation–aromatic sequences can be synthesized through cation– π complex-aided free-radical polymerization.

There are two prerequisites for the formation of such poly(cation-*adj*- π) (*adj* is an abbreviation for adjacent, and π denotes an aromatic monomer) polymers with controlled sequences:

Formation of cationic/aromatic complex by cation– π interaction in the polymerization precursor

solution; and the reactive vinyl heads of cationic and aromatic monomer pairs being the same ($R_1 = R_2$, see Figure 3). Despite containing 50% hydrophobic aromatic monomers, poly(cation-*adj*- π) has good solubility both in DMSO and water because strong electrostatic repulsion of the cationic residues prevents the hydrophobic aromatic residues from aggregating in polar solvents. In contrast, random copolymer poly(cation-*r*- π), which has cation- and aromatic-rich segments from $R_1 \neq R_2$ monomer pairs, is insoluble both in DMSO and water. In seawater, concentrated poly(cation-*adj*- π) formed a hydrogel, because salt ions screen long-range electrostatic repulsion and strengthen the effective cation- π and hydrophobic interactions between intra/inter-chains. The hydrogels exhibit fast, strong but reversible adhesion to diverse substrates, especially to negatively charged surfaces in seawater. Aromatics on copolymers are found to enhance the electrostatic interactions of their adjacent cationic residues to the counter surfaces even in a high ionic-strength medium. However, for a polymer without an adjacent sequence but similar composites, the resulting hydrogel exhibited very weak adhesion under seawater, which suggests that monomer sequences of polymers govern the properties of the corresponding hydrogels.

Besides the monomer sequence, the block sequence in copolymers also influences the properties of hydrogels.¹¹⁹ The gelation behavior of stimuli-responsive block copolymers with hydrophilic (A) and hydrophobic (B) segments were mostly studied in this case. It was found that block sequence always promotes the formation of a gel when compared to random copolymers.¹³¹⁻¹³⁴ Diblock copolymers form gels more easily than triblock copolymers, with no difference if the hydrophobic block is in the middle or at both ends,¹³⁵⁻¹³⁸ because diblock copolymers form more

stable micelles due to the low micellization enthalpy.¹³⁸ When comparing triblock terpolymers (ABA vs. BAB), the results are controversial; however, most of the studies show that the gelation temperature is lower for the ABA type.^{136, 139, 140} For the triblock terpolymers where the hydrophobic and the thermo-responsive monomers (C) are the outer blocks (BAC), the polymers form gels either at all temperatures or at lower gelation temperatures compared to the other two types of copolymers (BCA and ABC).^{131, 133}

With a precisely controlled sequence, biomacromolecules can assemble into ordered aggregate structures, for example, the double helix structure of DNA and β -folding of proteins. In hydrogels, polymer aggregation can be used as a crosslinker to connect the polymers into a network. As we mentioned above, the biomacromolecule-based hydrogels are typically crosslinked by the association of their biopolymer segments. However, compared with biopolymers, the majority of aggregation structures in synthetic polymers, e.g., hydrophobic micelles and coacervates of oppositely charged polymers, are disordered.^{38, 141-146} One exception is when using crystallizable polymers, which can form crystallites in the network under appropriate conditions.¹⁴⁷⁻¹⁴⁹ For instance, poly(vinyl alcohol) (PVA) hydrogel can be simply prepared from its solution by freeze-thaw cyclic processing.¹⁵⁰ This procedure results in the formation of PVA crystallites that work as physical crosslinks in the gel network. However, the crystallites in the network are randomly dispersed with diverse orientations, unlike aligned structures found in biosystems. Recently, Lin et al. proposed a strategy using mechanical training to achieve aligned crystallites architecture in PVA hydrogels.¹⁵¹ They prepared a PVA hydrogel

by using the freeze-thaw method followed by a cyclical pre-stretching process, during which the crystalline domains were directionally rearranged. As a result, the hydrogel achieved very high mechanical strength, high fatigue threshold, high water content, and a low Young's modulus, reaching combinational muscle-level properties.

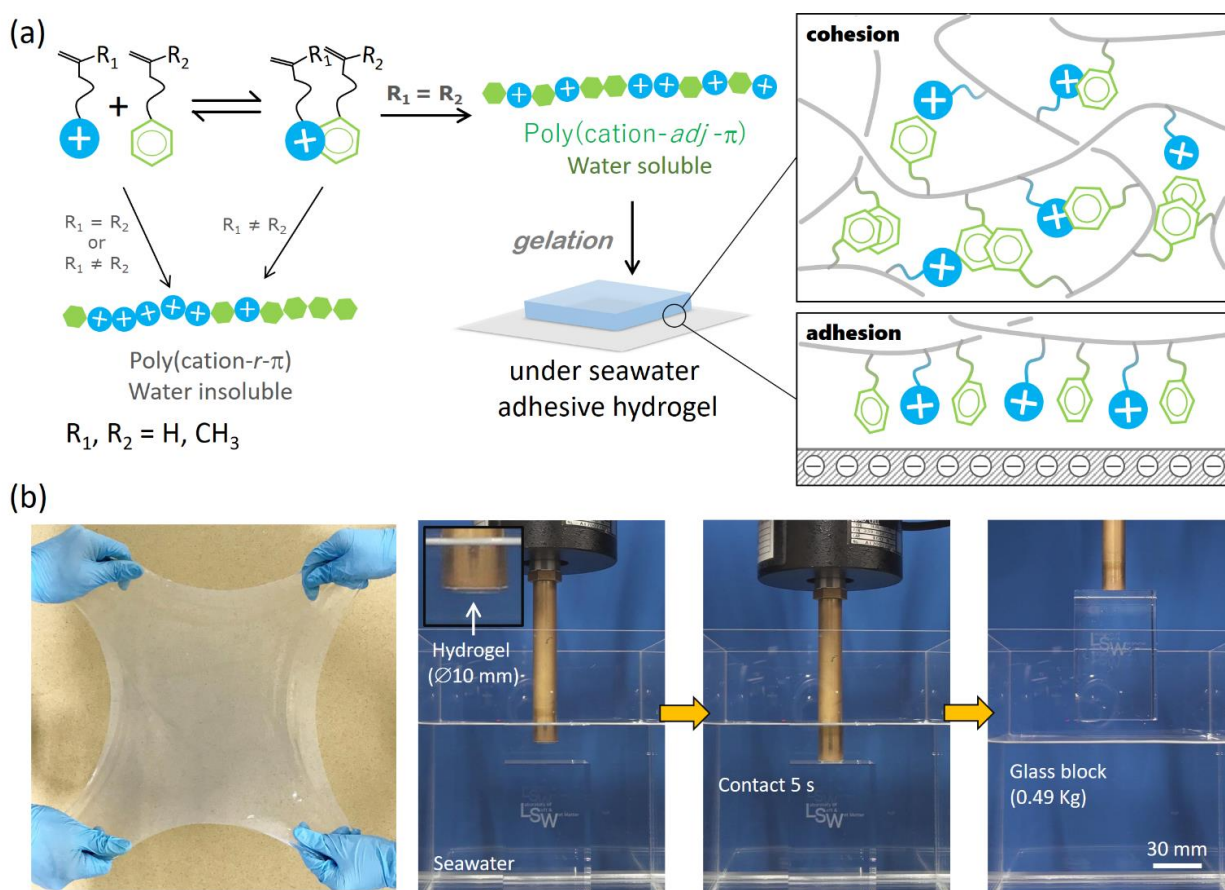


Figure 3. Functions through bioinspired monomer design and polymer sequence control.

Adhesive hydrogels with an adjacent cationic-aromatic sequence. (a) Cation- π complex-aided free-radical polymerization to synthesize poly(cation-adj- π) with adjacent cationic-aromatic

sequences and its supramolecular hydrogel showing electrostatic adhesion in seawater. (b) The photos of poly(cation-adj- π) hydrogel and its under seawater adhesion. Reproduced with permission from ref⁹¹. Copyright 2019 Springer Nature.

2.3 Hierarchical Network. The solid-like state of hydrogels is formed by the network structure through chemical or physical crosslinking between polymers. Synthetic hydrogels usually have heterogeneous polymer network structures with a wide distribution of the molecular weight of polymer strands between two cross-link points. One effect of such heterogeneity in structure are stress concentration points in the network during deformation, which results in poor mechanical strength.

One of the most successful studies to obtain a uniform network is performed by Sakai et al. who synthesized tetra-poly(ethylene glycol) (tetra-PEG) gels.³⁰ A tetra-PEG gel is prepared by the “cross-end-coupling” of two types of tetra-PEG macromers having mutually reactive terminal groups.^{152, 153} For example, it is considered that a combination of maleimide- and thiol-terminated tetra-PEGs can prepare a precisely controlled defect-free hydrogel.¹⁵⁴ The relatively mono-disperse network of a tetra-PEG hydrogel provides a good model system to study fundamental physical properties of hydrogels.¹⁵⁵⁻¹⁵⁹ Furthermore, by using this strategy, diverse tetra-polymer-based hydrogels with a mono-disperse network and functions have been developed.¹⁶⁰ For example, a “nonswellable” hydrogel without mechanical hysteresis,¹¹⁴ and a

degradable hydrogel without swelling under physiological conditions.¹⁶¹ Apart from tetra-PEG, other telechelic polymers or triblock copolymers with controlled molecular weight have also been used recently to build well-defined networks. These strategies have been the subject of recent comprehensive reviews.^{162, 163}

Slide ring hydrogel is another innovative example of a controlled network topology.²⁹ In its network, crosslinkers can move freely along the two chain axes within the polymer network. The sliding motion of the figure-of-eight crosslinkers accounts for the special properties of the slide ring hydrogels when compared with the conventional hydrogels, because, when the sample is stretched, the chains and crosslinkers can slide through each other to avoid localization of the stress.

Utilizing well-ordered metal-organic frameworks (MOFs) as a template is another strategy to synthesize network polymers with highly controlled structures.¹⁶⁴ MOFs are microporous crystalline materials that consist of organic linkers with bridging metal ions and organic ligands. When the organic ligand is reactive, it can be crosslinked or polymerized into a polymer network with highly organized structure.^{165, 166} Polyhedral gel particles developed by Kokado and coworkers are a unique example.¹⁶⁶⁻¹⁶⁸ In their method, called ‘crystal crosslinking (CC) method’, they used a reactive organic ligand to synthesize a MOF first, and then they introduced a crosslinker to crosslink the ligand, followed by demetallation. The obtained MOFs-templated polymer gel particles thus exhibited various geometric shapes. Based on this strategy, they further fabricated anisotropically swelling gels by using anisotropic MOFs.¹⁶⁹

On the other hand, natural hydrogels usually have multi-network structures to achieve very different functions that could not be simply predicted from their individual components by synergistic effects. For example, cartilages, which consist of collagen fibers and proteoglycan aggregates (PGA), show high strength and toughness while containing 70wt% of water. It is considered that the collagen fibers counteract tensile force; meanwhile, the brush-like PGA retains a large amount of water and resists external compression pressure. A double-network (DN) hydrogel is a synthetic example showing how a multi-network structure can have a striking synergistic effect on mechanical properties.²⁷ DN gels consist of interpenetrated polymer networks with contrasting physical properties: one network is rigid and brittle while the other network is soft and stretchable, and the rigid network is weaker (low fracture stress) than the soft network.³⁴ The toughening of DN gel is due to an internal fracture mechanism, having some common features with the fracture of bones, which are organic-inorganic hybrid composites. The rigid, brittle network serves as a sacrificial bond that fractures at relatively low stress, while the soft, stretchable network serves as a hidden additional length that sustains stress of a large extension afterward. This kind of mechanism also gives insight into the tough behavior of natural cartilages. However, unlike the natural tough materials that usually have the ability of self-healing, traditional DN gels from chemical networks cannot recover after damage. Recently, this drawback was overcome by extending the DN concept to self-healable networks using reversible bonds.^{141, 170-173}

Biological tissues, such as muscles and tendons, have a well-ordered, anisotropic structure.

Hydrogels with anisotropic superstructures at the macroscopic scale, as in biological tissues, are not readily available yet. To develop such hydrogels, using directional molecules as building blocks to induce self-assembled structures is not enough. Applying external fields, such as shear flow and magnetic field, to gel precursor solutions are found useful to aid the formation of an anisotropic structure at the macroscopic scale. A successful example is the fabrication of anisotropic hydrogel sheets consisting of periodic stacking of water-impermeable poly(dodecyl glyceryl itaconate) (PDGI) bilayers trapped inside isotropic polyacrylamide (PAAm) hydrogel matrix (Figure 4).¹⁷⁴⁻¹⁷⁸ The macroscopically anisotropic hydrogel, formed by applying shear flow to the precursor solution, exhibits many unique functions that are substantially superior to conventional hydrogels, such as structure color, unidirectional swelling, high toughness, and self-healing.

Another example is the work by Aid et al., who successfully embedded unilamellar titanate nanosheets (TiNS) within a hydrogel by utilizing a strong magnetic field.¹⁷⁹ Under strong magnetic field, TiNS tend to form cofacial nanosheet alignment in aqueous colloidal dispersions, which can be fixed in hydrogel using *in situ* vinyl polymerization. Due to the anisotropic structure, the hydrogel deforms easily under shear forces applied parallel to the embedded nanosheets yet resists compressive forces applied orthogonally. Utilizing this mechanical feature, the authors also developed a hydrogel actuator by using a lower critical solution temperature (LCST)-active polymers.¹⁸⁰ By changing the temperature, the distance between the nanosheets

rapidly expands and contracts but without substantial water uptake and release macroscopically; as a result, the hydrogel deforms quickly and significantly.

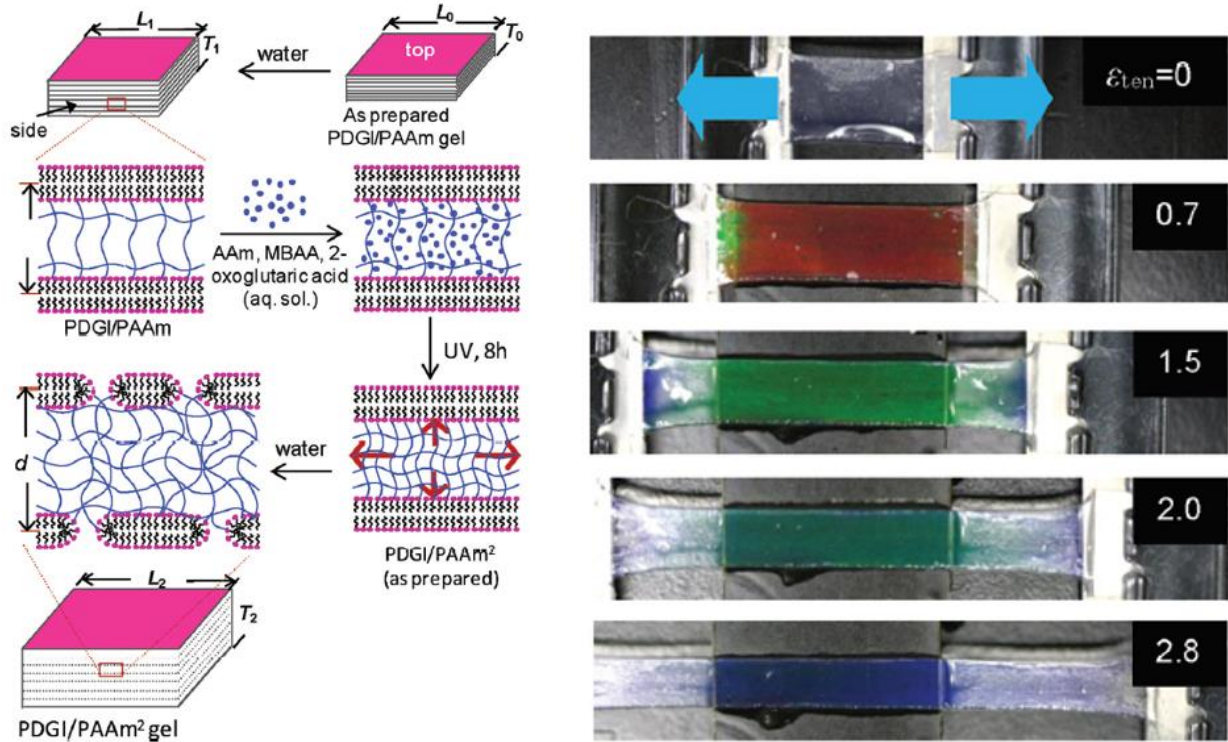


Figure 4. Functions through anisotropic order-disorder structure control. Bioinspired ultrafast color tuning of a photonic hydrogel. Reproduced with permission from ref¹⁷⁵.

2.4 Geometry and Morphology. Looking beyond the microscale of biological systems, the majority of structures in organisms also have complex macro geometry and morphology, which affect their biophysical characteristics and enable specific biological functions. Learning the

relationship between such macroscale structures and corresponding functions also provides us with design ideas and inspiration when designing functional materials. For example, in the human body, red blood cells (RBCs) having a biconcave discoidal shape, which enables them to deform thousands of times during their long circulation lives.¹⁸¹ Such an advantage is essential when designing drug delivery carriers with long circulation time. Inspired by the unique shape of RBCs, shaped stimuli-responsive hydrogel particles have been designed.¹⁸² For example, bovine serum albumin (BSA) based hydrogels with biconcave discoidal shape possess the ability to carry oxygen and can flow through capillaries smaller than their own diameter.¹⁸³ Merkel et al. found that RBCs shaped microgel particles with low modulus showed prolonged circulation time *in vivo*.¹⁸⁴ Moreover, mammalian epithelial and immune cells preferentially internalize disc-shaped, rather than nanorod-shaped hydrogel.¹⁸⁵ Apart from the unique shape of cells, compartmentalized organelles inside cells also perform distinct functions to maintain cell physiology. Inspired by this, multicompartment hydrogel particles have been developed.¹⁸⁶⁻¹⁸⁹

Another well-studied bio-geometry/structure is related to biological wet adhesive surfaces of organisms, for example, the arm of an octopus. In nature, many organisms can effectively attach to substrates or capture prey in water. By studying these organisms, several biomimetic adhesives have been developed in recent years.¹⁹⁰ For instance, inspired by macroscale suckers of octopus, Lee et al. demonstrated that smart adhesive pads enable excellent switchable adhesion in response to a thermal stimulus.¹⁹¹ They decorated a thermally responsive hydrogel layer on the elastomeric sucker surface, thus the cavity volume could be increased or decreased

via heating or cooling, respectively, resulting in a change in the cavity pressure. The smart adhesive pads can be used in transfer printing of semiconducting nanomembranes. Based on this adhesion strategy, Oh et al. fabricated a highly sensitive flexible temperature-sensor with bioinspired octopus-mimicking adhesive.¹⁹² In addition to thermal sensitive adhesion, wet-responsive smart hydrogel adhesive has also been reported.

Developing adhesives working on wet surfaces or underwater is another challenge, due to the existence of the hydration layer on the surface. In nature, the endoparasite *Pomphorhynchus laevis* can swell its proboscis to attach to its host's intestinal wall.¹⁹³ With this as an inspiration, Yang et al. developed a biphasic microneedle array that mechanically interlocks with tissue through swellable microneedle tips (Figure 5a).¹⁹⁴ To achieve this, the authors have chosen an amphiphilic block copolymer to build conical microneedles with a non-swellable inner hydrophobic region and swellable outer hydrophilic layer. When penetrating a tissue, the outer layer absorbs the water to achieve the interlock that strongly promotes the adhesion of the material. This design provides universal soft tissue adhesion, which has great potential in medical applications. In another example, recently, inspired by the geometry of the adhesive discs of clingfish, our group presented a design strategy to obtain hydrogels with fast, strong, and reversible adhesion underwater (Figure 5b).⁹² We patterned hexagonal structures on the surface of a polyampholyte hydrogel, resulting in surface grooves that not only accelerate water drainage and prevent water trapping but also delay crack propagation during detachment. Furthermore, at the nanoscale, the dynamic bonds of the gel form reversible bridges at the interface, as well as

dissipate energy in bulk during deformation. As a result, the patterned hydrogels exhibited excellent underwater adhesion on diverse substrates, including hard glasses, soft hydrogels, and biological tissues. This strategy of combining macroscale surface engineering and microscale dynamic bonds is applicable to various tough hydrogels.

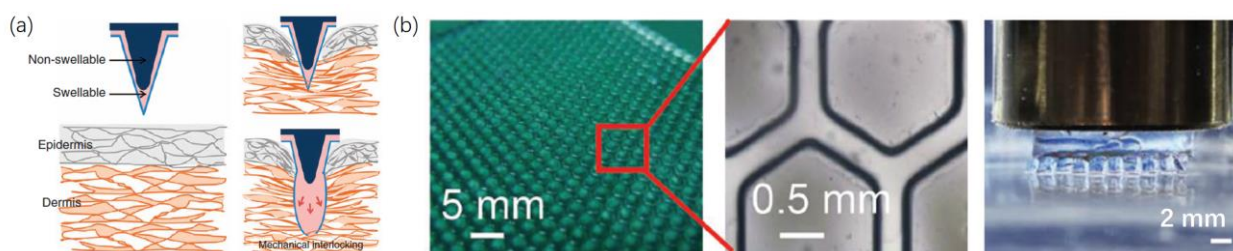


Figure 5. Functions through macroscopic geometry and morphology control. (a) Illustration showing mechanical interlocking of a water-responsive shape-changeable microneedle following penetration into tissue. Reproduced with permission from ref ¹⁹⁴. Copyright 2013 Springer Nature. (b) Photograph and optical microscopy image of the surface structures on a polyampholyte (PA) hydrogel, and photograph of patterned gels during debonding from a glass plate under water. Reproduced with permission from ref ⁹². Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA.

Moreover, inspired by the stomata in plant leaves, Gargava et al. designed a hydrogel film containing “smart” pores that can open and close based on the external stimuli, including

temperature, solvent composition, pH, and light, depending on the chemistry of the gel.¹⁹⁵

Schroeder et al. reported an electric-eel-inspired power concept that uses gradients of ions between miniature hydrogel compartments bounded by a repeating sequence of cation- and anion-selective hydrogel membranes.¹⁹⁶ This artificial electric organ is capable of generating potential differences in excess of 100 V. Another outstanding bio-geometry-inspired examples in recent years included leptocephalus-inspired hydrogel actuators capable of high-speed, high-force actuation with optical and sonic transparency in water,¹⁹⁷ bioinspired structure color hydrogel with self-healing ability,¹⁹⁸ and pufferfish-inspired long-term robustness hydrogel device that have high swelling ratio with high swelling speed and can be used as ingestible device for long-term gastric retention and physiological monitoring.¹⁹⁹

2.5 Out-of-equilibrium hydrogels. Today's hydrogels can show different responses to diverse kinds of external stimuli; however, such processes are still transitions from one equilibrium state to another. In contrast, biosystems utilize a different way to update themselves to adapt to the environment change while in the out-of-equilibrium state. For example, the muscle can autonomously grow or atrophy to adapt to their surrounding mechanical environment through metabolic processes. The development of real out-of-equilibrium hydrogels that possess adaptivity using metabolic-like processes is also a direction for the next generation of bioinspired hydrogels. Recent efforts made to imitate a “metabolic” process in a synthetic hydrogel showed that double-network hydrogel can be healed and even strengthened after repeated mechanical

training.²⁰⁰. In this system, the breakage of the network by mechanical stress is analogous to the muscle damage, and the monomers supplied from the outer environment are analogous to nutrients in a biosystem used for the formation of a new network (Figure 6). This work is the first example of realizing a continuous upgrade of the network under external stimuli with a muscle metabolism-like mechanism. Although this approach is still in its infancy, lacking the ability to remove the wastes as a biological metabolic process does, it will motivate further research on fabricating more complex systems analogous to living matter.

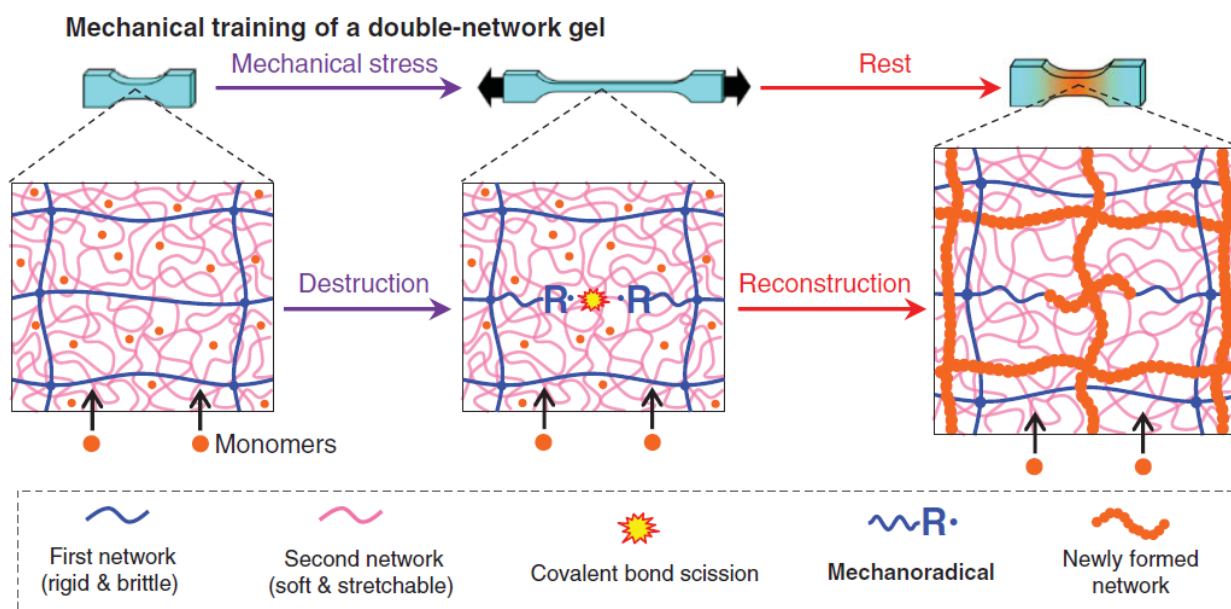


Figure 6. Functions inspired by muscle training. Self-growing materials based on mechanical training of DN gels. Mechanical stress leads to covalent bond breakage that generates mechanoradicals, and the mechanoradicals subsequently react with monomers supplied from the

outer environment to form a new network and strengthen the gel. Reproduced with permission from ref²⁰⁰. Copyright 2019 American Association for the Advancement of Science.

Self-oscillating hydrogels are out-of-equilibrium systems studied for years. These kinds of hydrogels are designed by utilizing the Belousov–Zhabotinsky (BZ) reaction in the polymer network to cause a chemical oscillation. By introducing ruthenium tris(2,2'-bipyridine) ($\text{Ru}(\text{bpy})_3^{2+}$), a catalyst for BZ reaction, into poly(N-isopropylacrylamide) (PNIPAAm) network, the poly(NIPAAm-co- $\text{Ru}(\text{bpy})_3$) gel swells and deswells at the oxidized and reduced states of $\text{Ru}(\text{bpy})_3$, respectively.²⁰¹ Based on this concept, many types of biomimetic or smart material systems have been developed, which have been thoroughly reviewed in the literature.²⁰²⁻²⁰⁴

3. PERSPECTIVES AND OUTLOOK

Over the last two decades, looking to nature for inspiration when developing novel functional hydrogels has resulted in remarkable progress. By analyzing biosystems from the molecular design to macroscopic geometry, numerous bioinspired hydrogels with diverse functionalities have been fabricated. However, compared with natural hydrogels, man-made systems are still in their infancy. Looking from nano- to macroscopic scale, synthetic hydrogels are far behind biosystems, and we are only scratching the surface of the possibilities in mimicking biological structures. In fact, the prerequisite for the elaborate structure of biological materials is their

precisely controlled monomer sequences of biopolymers. Therefore, the fundamental problem of polymeric materials is the precise control of polymer structure, which is still the central challenge in polymer chemistry. Although the development of synthetic polymers with controlled monomer sequences has made great progress in the past decade, the challenges still remain in making precisely controlled sequences using the high-efficiency synthesis of polymers for mass production to meet the demand for these materials, as well as in the characterization of sequences in obtained polymers.^{205, 206} In contrast, biosystems are assembled precisely at all scales, from monomer to network, to construct hierarchical structures with specific geometries, which enables the organs to fulfill different functions. However, most of the synthetic hydrogel imitations of biosystems are still too simple and are limited to one scale. Tomorrow's bioinspired hydrogels should be more complex; they should not only have precisely controlled monomer sequence but also a hierarchical network structure at multi-scales (micrometer to millimeter). To achieve this, a combination of self-assembly and phase separation processes using external fields, such as tensile stress, shear flow, extrusion, electric and magnetic fields, could be used. We believe that the research on bioinspired hydrogels will enable the next generation of artificial tissues and various soft artificial organs, which will substitute hard artificial organs such as artificial blood vessels and the artificial heart.

On the other hand, although the excellent function of soft living tissues is attributed to their high water content and elaborate structures, the scientific explanations of these functions are still lacking. The high-performance hydrogels created through learning from nature can lead us to

revealing the mechanism of *emergent functions* demonstrated in biological systems, thus answering the question what special functions various structures in living tissues have. These studies will firmly establish a new subfield in soft matter that is characterized by molecular transportation, large deformation, non-linearity, relaxation, out-of-equilibrium processes, and mechanochemical reaction: *Soft & Wet Matter Science*.

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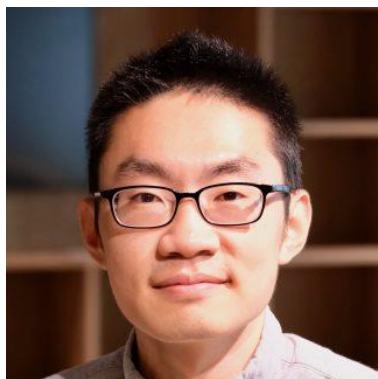
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Notes

The authors declare no competing financial interests.

Biographies



Hailong Fan received his BS (2011), MS (2014), and Ph.D. (2017) degrees from Renmin University of China. He then joined Prof. Jian Ping Gong's group at Hokkaido University as a postdoctoral research fellow in 2017. In April 2020 he was promoted to an assistant professor in WPI-ICReDD at Hokkaido University. His current research focuses on functional hydrogels with controlled monomer sequences.



Jian Ping Gong is a distinguished professor of Hokkaido University, Japan. She graduated from Zhejiang University, China, and received a Doctor of Engineering degree at Tokyo Institute of Technology. She joined the faculty at Hokkaido University in 1993. She has been focusing on novel hydrogels with high mechanical performance, including double network hydrogels with high strength and toughness, self-healing hydrogels, low surface friction hydrogels, and hydrogels with underwater adhesion. Currently, she is focusing on functional hydrogels inspired by biological systems, including self-growing hydrogels, thermal stiffening hydrogels, marine adhesive hydrogels, and memory-forgetting hydrogels. She is also working on the applications of the double network hydrogels as artificial cartilages. She received several awards including Wiley Polymer

Science Award (2001), The Award of the Society of Polymer Science, Japan (2006), The Chemical Society of Japan Award (2011), The DSM Materials Sciences Award (2014), and the MEXT Commendation for Science and Technology, Japan (2019).

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