Feature Article for POLYMER

Super tough double network hydrogels and their application as biomaterials

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Abstract

The double-network (DN) technique, developed by authors' group, provides an innovative and universal pass way to fabricate hydrogels with super high toughness comparable to rubbers. The excellent mechanical performances of DN hydrogels originate from the specific combination of two networks with contrasting structures. The first brittle network serves as sacrificial bonds, which breaks into small clusters to efficiently disperse the stress around the crack tip into the surrounding damage zone, while the second ductile polymer chains act as hidden length, which extends extensively to sustain large deformation. Based on the principle of DN hydrogel, the author's group recently has developed several novel systems and techniques, which has greatly expanded the practical accessibility of DN technique for practical use. The DN principle and the DN gel have already attracted much attention in the soft matter community. Inspired by the DN principle, many research groups have also designed and developed some innovative hydrogels with large enhancement in their mechanical strength and toughness. Some tough hydrogels fabricated by the DN technique also exhibit good biocompatibility and low friction resistance with promising prospective in industrial and medicine fields, especially for load-bearing artificial soft tissues such as artificial cartilage. In this feature article, we address the major concept and toughening mechanism of DN gel, then we describe some recent novel hydrogel systems based on the DN concept, and finally the applicability of DN gel as soft biomaterials is discussed.

1. Introduction

Hydrogels, which are soft and wet materials, usually composed of three dimensional polymer network structure and large amount of water (50-99%) inside the network structure and have potential applications in many fields. Beside their wide variety of applicability such as drug delivery system, superabsorbants, microfluidics, and contact lenses in the materials science domain, they have become extensively attractive in tissue engineering because of their stimuli responsive property [1-19]. However, most of the synthetic hydrogel suffered from a lack of mechanical strength compared with the hydrogel-like bio-tissues such as cartilage, tendon, muscle, and blood vessel [20]. These load-bearing soft tissues exhibit excellent mechanical performances, for example, cartilage tissue possesses high toughness, shock absorbing, low sliding friction [21]. Seeking artificial tissues (excellent soft, wet, and tough hydrogel material) as a replacement of damaged ones has been a challenging task for material scientists.

Over past 10 years, several hydrogels with excellent mechanical performance have been successfully developed [22-26]. Soft and highly extensible gels with a relatively homogeneous network structure are developed by using sliding cross-linkers (slide ring, SR, gel) [22], or by using two kinds of tetrahedron-like macromonomers (tetra-PEG gel) [23]. These gels exhibit an ideal elastic deformation. On the other hand, high modulus and high toughness gels with composite structures are developed by combining clay with polymer (nanocomposite, NC, gel) [24], or by combining a rigid and brittle network with a soft and ductile network (double network, DN, gel) [25, 26]. The former one has shown effective improvement of mechanical strength while the latter one (DN gel, which was developed by author's group) has exhibited the highest fracture toughness.

The double network (DN) gels possess interpenetrating polymer network (IPN) structure where the properties of two networks existing in sharp contrast such as network density, rigidity, molecular weight, cross-linking density etc. They are generally synthesized via a two-step sequential free-radical polymerization process in which a high relative molecular mass neutral 2nd polymer network is incorporated within a swollen heterogeneous polyelectrolyte 1st network [25]. The mechanical properties of DN gels prepared from many different polymer pairs were shown to be much better than that of the individual components. Under an optimized structure, the DN gels, containing about 90 wt% water, possess hardness (elastic modulus of 0.1–1.0 MPa), strength (failure tensile stress 1~10 MPa, strain 1000–2000%; failure compressive stress 20–60 MPa, strain 90–95%), and toughness (tearing fracture energy of 100–4400 J·m^{-2}) [26, 27–34]. These excellent mechanical performances had never been realized before in synthetic hydrogels, and are comparable to and even exceed some soft load-bearing tissues [21].

Enhancement in mechanical strength by the double network concept has been observed in some other works of authors' group as well as other groups. Combination of bacterial cellulose (BC) with neutral polymers, such as gelatin, or synthetic polymers also exhibits an enhanced mechanical performance [35, 36]. Similarly, based on the DN principle, the authors' group have developed several novel systems with enhanced mechanical property and techniques such as void-DN gel [37], microgel-reinforced particle DN gel [38], liquid crystalline DN gel [39], ultrathin DN gel [40], bilayer incorporated tough gel [41,42], free-shaped tough DN gel [43], bonding of one gel to another gel or solid substrate [44], etc. that should greatly expand the diversity of DN principle. Inspiring with the DN concept, other groups have also developed some novel interpenetrating polymer network (IPN) systems such as poly(ethylene glycol)/poly(acrylic acid) (PEG/PAAc) [45-47], poly(ether-

urethane)/poly(methyl-methacrylate) (PEU/PMMA) [48], agarose/poly(ethylene glycol) diacrylate [49]. The IPN systems are developed from two different polymers with similar properties. As, in principle, DN gel also possesses IPN structure and above mentioned IPN systems were developed by applying DN concept, all the IPN gel systems are defined as DN gel in this article. Some other DN gel systems such as the modified hyaluronan/poly(N,N'-dimethylacrylamide) (PHA/PDMAAm) [50], jellyfish/polyacrylamide (JF/PAAm) [51] have also been reported by other research groups. Recently, Zhang et al. synthesized DN hydrogel from two biocompatible polymers [52]. These entire DN systems exhibit enhanced mechanical strength and toughness much better than that of the individual components and most of them possess fracture stress and toughness in the order similar to the soft bio-tissues.

In this feature article, we first address the main concept of tough DN gel, including the method of preparation, structure, mechanical feature and the toughening mechanism. Then, we discuss how the DN concept helps to develop above mentioned novel DN gel systems by the authors' group as well as other groups. Finally we discuss the applicability of those synthetic hydrogels as biomaterials, *i.e.*, as a replacement of natural cartilage or others.

2. A short review of double network (DN) gel

2.1 Method of preparation

The DN gels are generally synthesized via a two-step sequential free-radical polymerization process [25]. In the first step, a hydrogel composed of tightly cross-linked network structure of rigid and brittle polyelectrolyte is formed. This brittle gel is subsequently swelled in an aqueous solution of a neutral monomer and then the monomer is polymerized to form a loosely cross-linked, flexible network inside the first brittle gel. The obtained hydrogel so-called DN hydrogel is immersed in water again to reach the equilibrium swelling state.

2.2 Structure

The DN gels are comprised of two independently cross-linked networks. An optimal combination has been found when the first network is a rigid polyelectrolyte and the second one is a flexible neutral polymer. The optimum feature of two kinds of polymers with strong contrast structure are; (a) rigid and brittle polymer as the first network, such as polyelectrolyte; soft and ductile polymer as the second network, such as neutral polymer, (b) the molar concentration of the second network is 20–30 times the first network, and (c) the first network is tightly while the second network is loosely cross-linked, which requires a very high molecular weight of the second polymer [26,27]. In a word, the delicate balance between a suitable brittleness of the first network and a ductility of the second network is preserved to obtain the anomalous DN structure of the hydrogel. We should note here that the strong contrast properties of the two networks in DN gels make them quite different from the conventional interpenetrated network (IPN) gels. It is found that the dramatic increase in the mechanical strength of the DN gels occurs above the region where linear PAAm chains are entangled with each other and the entanglement between the second component PAAm plays an important role of the toughening mechanism of DN gels [27]. The high strength of DN gels is due to a synergistic effect of the binary structure rather than a linear combination of two component networks, like the conventional IPN or fiber-reinforced hydrogels [53].

2.3 Mechanical feature

So far, the DN gels synthesized with poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS) polyelectrolyte as the first network and polyacrylamide (PAAm) neutral polymer as the second network stands out with unusual properties and serves as the system for further studies. At an optimal composition, the PAMPS/PAAm DN gels show excellent mechanical

performance, although they include ~90 wt% of water. The compressive fracture stress of the DN gels achieves several dozens of MPa, which is comparable to that of cartilage. In addition, the tearing energy reaches up to 4400 J/m^2, which is several thousand times of that of single network PAMPS and PAAm hydrogels [27-31,34]. During the tensile test, tough DN gels usually show remarkable necking phenomenon, as shown in **Figure 1a**. Narrowed zones appear in the sample at a certain strain, $\varepsilon \sim 2$ mm/mm, and grow up to with further elongation [26,28,54,55]. In the stress-strain curve, yielding occurs and a plateau region appears during the neck zone propagation, which is insensitive to strain rate. After the necking, the gel becomes very soft with an elastic modulus approximately 1/10 of that before the elongation test [56]. It was confirmed that the first PAMPS network breaks into small clusters even at several percent of strain because of the intrinsic fragile properties of PAMPS single network hydrogel. These clusters play a role of physical cross-linker of long flexible PAAm chains (second PAAm network is loosely cross-linked). The fragmentation during the elongation involves dissipation, which is reflected in the hysteresis of the second loading curve (**Figure 1a**) [26,55,57]. The necking phenomenon can be regarded as a damage accumulation of the first network; on the strongly stretched region, the gels transform into a very soft one by breaking the first network into small clusters (**Figure 1b**). Both the fragmentation of PAMPS network and chain-pulling process of flexible PAAm chains from the clusters dissipate energy, endowing the DN gel with toughness. However, the former is predominant in the case of the DN gel, which is the reason why the mechanical behaviors (strength and toughness) are hardly influenced by the strain rate [26,28,32,56]. Besides the tensile test, tearing test as a measurement of the fracture energy is applied to qualify the mechanical strength of the DN gels (**Figure 2a**) [30,32,55]. The tearing energy T of PAMPS/PAAm DN gels ranges from 10^2 to 10^3 J/m^2 [34,55], which is 100-1000 times larger than that of single network PAAm gels (~10 J/m^2) or PAMPS gels (~0.1 J/m^2) with the similar polymer

concentrations to those of DN gels. It should be noted here that the tearing energy T, defined as the energy required for fracturing a unit area in a sample, was calculated by $T=2F_{ave}/w$, where F_{ave} is the average tearing resistance force, and w is the width of the gel. The tearing energy thus defined is 2 times of the fracture energy G used in previous papers [29-31].

2.4 Toughening mechanism

The fundamental toughening mechanism of the DN gel is well understood by the tearing test of a trouser-shaped sample with a pre-existing crack (**Figure 2a**). During the tearing test, a large damaged zone (yielding zone) was appeared around the crack tip. Therefore, significantly high toughness of the DN gel originates from the emergence of the large damaged zone (yielding zone) around the crack tips that has been directly observed under a color three-dimensional violet laser scanning microscope (**Figure 2b**) [32,59]. In the fracture process of the DN gels, the stress concentrated at the crack tip efficiently causes an internal fracture of the first network around the crack tip, which remarkably dissipates energy, and therefore greatly enhances the fracture propagation resistance (**Figure 2c**). The internal fracture of the DN gels comes from the fragmentation of the brittle first PAMPS network, whereas the ductile PAAm chains entangled with the fractured PAMPS clusters are stretched without breaking up to a quite large extension [26,56,58,60]. Therefore, the toughening mechanism, that is, the anomalously large fracture energy of DN gels, is attributed to the necking phenomenon, whereupon the first brittle network serves as *sacrificial bonds*, which breaks into small cluster to efficiently disperse the stress around the crack tip into the surround damage zone, while the second ductile polymer chains act as *hidden length*, which extends extensively to sustain large deformation. The structure change, i.e., fragmentation of the first network, is accumulative and irreversible. Formation of large yielding or fracture

zone at the crack tip seems to be a common feature for the tough materials, such as in the fracture of natural bones [61].

Small-angle neutron scattering (SANS) was applied to investigate the molecular origin of the toughness in DN gels [62]. SANS data taken on the deformed state of the DN gel demonstrates the occurrence of compositional fluctuations from both linear PAAm chains and the PAMPS network when DN gels are deformed. The length scale of this deformation induced feature with a periodicity at micrometer length scale (~1.5 μm) can occur only if the deformation process is self-regulating in nature. A self-regulating process can lead to the observed increase in fracture toughness of DN gels because the development of a regularly repeating structure offers an energy dissipating mechanism throughout the entire sample volume instead of being concentrated at the crack tip, which results in run-away fracture [62]. The DN gels are much tougher than the single network gels and their toughness are comparable with various polymer materials such as rubber, plastics (**Figure 2d**). The tough DN hydrogels have been highlighted in a recent review article which described the comparable fracture energy of DN gel with those of rubbers, plastics, metals, glasses etc in terms of their enhanced mechanical performance and their corresponding toughening mechanism [63].

Inspired with this DN principle, several novel hydrogel systems have been developed by the authors' group as well as other groups in recent years such as cellulose based anisotropic DN gel [35,36], void-DN gel [37], microgel-reinforced particle DN gel [38], liquid crystalline DN gel [39,41,42], poly(ethylene glycol)/poly(acrylic acid) inverse DN gel [45-47], poly(ether-urethane)/poly(methyl-methacrylate) [48], agarose/poly(ethylene glycol)-diacrylate [49], the modified hyaluronan/poly(N,N'-dimethylacrylamide) [50], and

jellyfish/polyacrylamide [51] gels. The enhanced mechanical strength, toughness, and their applicability as a biomaterial are discussed in the following sections.

3. Other hydrogel systems inspired by double network concept

3.1 Anisotropic double network gel based on bacterial cellulose

On the base of DN principle, biocompatible anisotropic hydrogels with a high mechanical strength has been synthesized by using natural polymer, bacterial cellulose (BC). BC is extracellular cellulose, produced from bacterium acetobacter consisting of hydrophobic ultra-fine fiber network stacked in a stratified structure [64]. Due to this unique structure, it shows mechanically anisotropic property. Double network (DN) gels based on BC were prepared by applying the double network principle. At first, the first network (BC) gel was prepared **[**65**]** and the obtained BC gel was then immerged in an aqueous solution of 2nd monomer such as gelatin, AAm until equilibrium. The second network in the BC gel was formed by polymerization in presence of chemical cross-linker [35]. An as-prepared BC containing 90% water, however, the water is easily squeezed out and no more recovery in the swelling property, due to the hydrogen-bond formation between cellulose fibers (**Figure 3, 1st column**). On the other hand, gelatin gel is brittle and it is easily broken into fragments under a modest compression of 0.1 MPa (**Figure 3, 2nd column**). In contrast, the BC/gelatin DN gel can hold water even under such high pressure as 3.7 MPa and completely recovers the original shape by repeated compression (**Figure 3, 3rd column**).

The typical compressive stress-strain curves of BC, gelatin, and their composite BC/Gelatin double network (DN) gels are shown in **Figure 4a**. The compression is applied in the direction vertical to the stratified structure of BC and BC/gelatin gels. Due to unique stratified structure, BC gel shows mechanically anisotropic property with a high tensile modulus (2.9 MPa) along the fiber layer direction but a low compressive modulus (0.007

MPa) in perpendicular to the stratified direction [35]. The BC/gelatin DN gel shows a different stress-strain profile comparing to those of individual BC and gelatin gels. The fracture strength of BC/gelatin DN gel against compression reaches 3.7 MPa, which is about 31 times higher than that of gelatin gel (0.12 MPa) (**Figure 4a**). The composite gel shows a compressive elastic modulus of 1.7 MPa in the direction perpendicular to the stratified structure, which is more than 240 times higher than that of BC (0.007 MPa) and 11 times than that of the gelatin gel (0.16 MPa) [35].

The tensile stress-strain curves of the BC, gelatin, and BC/gelatin DN gels along the direction of the stratified layer are demonstrated in **Figure 4b**. At room temperature, the water swollen BC/gelatin DN gel (swelling degree ~5.8) can sustain stress nearly 3 MPa, and shows the elastic modulus of 23 MPa, which is 112 times larger than that of the gelatin gel. From the cyclic compressive test, it is seen that BC could not show its original stress-strain profile. While the BC-gelatin DN gel recovers well from compressive deformation after second testing under a repeated compressive stress up to 30% strain [35]. Thus, the double network structure led to a substantial improvement of the mechanical properties in tensile strength as well. Similar improvement in the mechanical strength was also observed for other combinations with polysaccharides, such as sodium alginate, gellan gum, and ι-carrageenan [35].

A great improvement of the mechanical properties of a BC gel has been noted by combining BC with PAAm (BC/PAAm) using the DN technique which sustains not only high compression but also high elongation. By controlling the water content of the BC gel prior to polymerization of the second (PAAm) network, a ligament-like tough BC/PAAm DN gel with tensile strength of 40 MPa was successfully obtained [34,36].

3.2 Inverse double network hydrogel

Recently, Frank's group has developed an interpenetrating polymer network (IPN) system, which is, in effect, the "inverse" of the DN gels developed by Gong et al., by applying DN principle [66-69]. Specifically, the first network is composed of a neutral end-linked poly(ethylene glycol)-diacrylate (PEG-DA) macromonomers with defined average molecular weight. The second network is, in contrast, a loosely cross-linked, ionizable network of PAAc. The inverse DN hydrogels were synthesized by a (two-step) sequential network formation technique based on UV-initiated free radical polymerization. The first hydrogel network (PEG-DA) was prepared by the reaction between PEG and acryloyl chloride. To incorporate the second network, the PEG-DA hydrogel was immersed in an acrylic acid (AAc) monomer solution containing photo-initiator solution and cross-linking agent for 24 hr. The swollen gel was polymerized by UV and cross-linked to form the interpenetrated polymer network structure. PEG and PAAc networks are both relatively fragile materials, so neither would be expected to make the sole contribution to mechanical enhancement. The two polymers form complexes through hydrogen bonds between the ether groups on PEG and the carboxyl groups on PAAc [70]. This interpolymer hydrogen bonding enhances their mutual miscibility in aqueous solution, which, in turn, yields optically transparent polymer blends. The compressive stress-strain curves of the PEG and PEG/PAAc gel are shown in **Figure 5a**. The single PEG gel possesses low compressive fracture stress and strain as 0.5 MPa and 40%, respectively. In contrast, the compressive fracture stress and strain of the DN gel was dramatically improved by forming DN with PAAc as 8 MPa and 90%, respectively. The moduli of the PEG single networks gel was magnified in the PEG/PAAc DN gel and the stress-strain curve of the DN gel makes the transition from the initial modulus to the strain-hardened final modulus (**Figure 5a**). The strain-hardening behavior in the PEG/PAAc system is particularly pronounced under conditions where hydrogen bonding is possible (low pH and pure water). On the other hand, the DN gel's strain harden and, in turn, become "pre-

stressed" with high values for initial Young's moduli when swollen in buffers of physiologic pH and salt concentrations (*i.e.* phosphate buffered saline (PBS)). The strain hardening under these conditions is the result of the constraining effect that the tightly cross-linked, neutral PEG network has on the swelling of the ionized PAAc network. This constraining effect leads to additional physical cross-links between the two networks and manifests as an increase in the initial Young's modulus of the DN [45]. The interpenetrating networks of PEG/PAAc gel have been explored as vehicles for drug delivery and as chemomechanical systems due to their reversible, pH-dependent swelling behaviour [69,71,72].

The molecular dynamic simulation of PEG/PAAc DN hydrogel system for mechanical property has been investigated by Goddard *et al.* [47]. Molecular dynamic simulations for PEG/PAAc DN gel were carried out similarly to the DN network formation process. The detail procedure has been described elsewhere [47]. Molecular dynamic simulations of PEG/PAAc DN hydrogel system at normal state and elongated state (300%) are shown in **Figure 5b**. The stress-strain curves from uniaxial extension simulation are presented in **Figure 5c.** The PEG/PAAc DN hydrogel has a sudden increase of stress above 100% strain, which is much larger than both SN hydrogels at the same strain. The stress of the DN hydrogel is found almost equal to the linear sum of the stresses of the two SN hydrogels at a strain of <100%. This means that, up to a strain of 100%, the two-component networks deform independently within their cross-linked structure without significant interaction between these two networks. In contrast, with a strain of >100% shows very different the stress of the PEO-PAA DN hydrogel increases very rapidly as a function of strain. This indicates that the cross-linking becomes effective at a strain above 100%. It can be concluded that molecular simulations of the PEG/PAAc DN hydrogel provides the

mechanical property in good qualitative agreement with the experimental observations [25,35,45].

3.3 Other double network gel systems

Chen *et al.* have prepared double network (DN) hydrogels based on hyaluronan (HA) and poly(N,N'-dimethylacrylamide) (PDMAAm) by a two-step photo cross-linking process [50]. Methyacrylate groups were first introduced onto HA chains and photo cross-linked to prepare the first hydrogel network (photo cross-linked hyaluronan, PHA). The second network PDMAAm subsequently formed by photo cross-linking in the presence of the first formed PHA network (*i.e.*, PHA/PDMAAm). By SEM observation, PHA hydrogel exhibited the largest pore size (average: 50 μm) whereas, due to the presence of the second PDMAAm network, which increased the relative cross-linking density of the hydrogel structure, the PHA/PDMAAm hydrogel appeared to have more compact porous structures with an average pore size ranging from 10 to 20 μm (**Figure 6a,b**). The stress-strain behavior of PHA, PDMAAm, and PHA/PDMAAm hydrogels under uniaxial compression are shown in **Figure 6c**. Pure PHA and PDMAAm single network hydrogels fractured at stresses 0.29 MPa and 0.04 MPa, respectively, while the PHA/D-3-0.05 possessed a fracture stress of over 5.25 MPa. The fracture strain of PHA/D-3-0.05 hydrogel was 87.1%, which was considerably higher than that of either the PHA (56.1%) hydrogel or the D-3-0.05 (78.4%) hydrogel. Due to the synergistic effect produced by double network (DN) structure, despite containing 90% of water, the resulting PHA/PDMAAm hydrogel possesses greatly enhanced mechanical properties as compared to the single network PHA hydrogel; the loosely cross-linked second network dissipates stress during compression contributing to the high mechanical strength of the double network hydrogel. Compared to the photo cross-linked hyaluronan single network

hydrogel, which is generally very brittle and fractures easily, the PHA/PDMAAm hydrogels are ductile. The mechanical effect produced by a DN structure [25] suggested that one of the networks contributed to the elastic stress, whilst the other one contributed to the strain. The stress-strain profiles obtained indicated that the PHA hydrogel was brittle whilst the PDMAAm hydrogel was more ductile. Therefore, it could be inferred that the brittle PHA network in PHA/PDMAAm contributed to the elastic stress and the PDMAAm network contributed to the strain of the double network hydrogel [50].

Based on the Double network (DN) principle, Lanir *et al*. [48] have reported poly(ether-urethane)/poly(methyl methacrylate) interpenetrating polymer networks (PEU/PMMA) gel under bulk polymerization conditions. Introduction of DN or IPN greatly improved the hydrogels' strength up to a modulus of 10 MPa similar to the cartilage [48]. A new method for encapsulating cells in DN hydrogels of superior mechanical integrity was developed by Gehrke's group [49]. In this study, two biocompatible materials, agarose and poly(ethylene glycol) (PEG) diacrylate, were combined to create a new DN hydrogel with greatly enhanced mechanical performance. Unconfined compression of hydrogel samples revealed that the DN displayed a fourfold increase in shear modulus relative to a pure PEG-diacrylate network (39.9 vs. 9.9 kPa) and a 4.9-fold increase relative to a pure agarose network (8.2 kPa). PEG and DN compressive failure strains were found to be 71% and 74%, respectively, while pure agarose gels failed around 15% strain [49]. However, in most of these works, little information on the mechanical behaviors of these gels under the tensile test or the tearing test, which tells the true toughness of the materials, are presented.

4. Recently developed double network gel systems

4.1 Jellyfish gel

Very recently, *Wang et al.* have fabricated a new type of DN hydrogel by introducing a synthetic hydrogel into a biological hydrogel which is directly obtained from an animal body, jellyfish (JF) gel, considering double network principle. The JF gel was put into an aqueous monomer solution with or without a cross-linker MBAA and then the sample was irradiated with ^{60}Co-γ rays, resulting in a novel type of DN hydrogel with very high mechanical strength [51]. The JF DN gel combine the well-developed structure of biological jellyfish gel and the unique microstructure of the synthetic gel produced by the radiation method, and strong interactions between the two networks are formed. The fabrication process of the JF DN gels and the microstructures of JF gel and JF DN gel are proposed in **Figure 7a**.

Jellyfish gel has quite high compressive and tensile strengths even with a very high water content of 99 wt.%. When freeze-dried the jellyfish gel has a layered porous structure and its pore walls consist of nano-structured layers with many fibers connected to the layers. Presumably a similar structure remains when the material is water swollen as it is optically cloudy. The well developed microstructure provides the mechanism for the jellyfish gel to disperse stress on it and hence suppress stress concentrations at flaws and crack tips. The tensile stress-strain curves for the JF/PAAm and PAAm gels are shown in **Figure 7b**.The JF/PAAm gel had several to several ten times higher tensile and compressive moduli, fracture stress, fracture strain than those of the JF gels and the corresponding PAAm gels indicating that there must have been considerable interaction between the two networks in the gel, *i.e.* bridged between the two components of the gel by the DN formation [51].

4.2 Double network gel with soft void structure inside

Although DN gels show excellent properties, their strength and toughness are lower than those of the widely used filler-reinforced rubber. For wide application to both medical and

industrial fields, further toughening of DN gels is required. Here, a common toughening method for general polymeric materials is introduced to improve the toughness of DN gels. It is seemed that soft spherical elastomers in hard material enable to enhance the toughness, though it depends on several factors [73,74]. The method of introduction of soft spherical structure into DN gels has been applied to increase their toughness. First, the first network PAMPS gels with dispersed silica nanoparticle were polymerized. After that particles in the gels were dissolved by hydrofluoric acid (HF) to obtain the PAMPS gels with the hollow void structure (void-PAMPS gels). Second, the second PAAm network was formed in the void-PAMPS gels by polymerization to obtain void-DN gels, which have the hard PAMPS/PAAm body and the soft spherical PAAm void [37]. The synthetic pathway and the structural model of void-DN gels are shown in **Figure 8**.

Figure 9a shows the tensile stress–strain curves of the DN gels with the void structure (called void-DN gels) with different void density [when void diameter, L = 200 nm]. The stress–strain curves strongly depended on the volume fraction of the void, ϕ. The fracture energy of the void-DN gels also strongly depended on ϕ and L, because the tearing energy (T_{void}) of the void-DN gels are nearly equal with that of the DN gel without void (T_0) when the void diameter (L) was much smaller than the Flory radius of the PAAm chains (R_F) [**Figure 9b**]. In contrast, T_{void} became twice of T_0 when L was much larger than R_F [**Figure 9b**]. Such toughening was induced by wider range of internal fracture of the PAMPS network derived from partial stress concentration near void structure which is discussed as follows.

It has been found that (i) when the first PAMPS network of the DN gel is synthesized, some divinyl-cross-linker MBAA are reacted only on one side and the other end (double bond) remained unreacted in the first PAMPS network; (ii) when the second PAAm is synthesized in the first PAMPS gels, AAm and the remained double bonds are copolymerized,

i.e., the second PAAm is chemically cross-linked with the first PAMPS gels [31]. Hence, some PAAm chains in the void-DN gels are also chemically connected with the PAMPS chains depending on the void's parameters. So, in accordance with the DLS result [37], the PAAm chain distribution around the void can be drawn as **Figure 9c and 9d.** If $L<R_F$, the PAAm chains inside the void connect with the PAMPS chains around the void. So, the void is bridged with the PAMPS chains by several PAAm chains. On the other hand, if $L>R_F$, the PAAm chains are so short that they cannot bridge the void structure with the PAMPS network. In the former case, the gel did not have a ''true'' void structure, which did not toughen the void-DN gels. On the contrary, in the latter case, the void structure forms ''true'' void structure *i.e.*, no link with PAMPS network, which toughened the void-DN gels. In short, it is possible that the presence of true void structure is crucially important for toughening of DN gels.

4.3 Microgels-reinforced double network gel

The reinforcement mechanism of double network (DN) gels has been extensively studied, and it has been elucidated that the rigid and brittle polyelectrolyte network serves as sacrificial bonds to increase the resistance against the crack propagation by forming a large damage zone at the crack tip [55]. From this DN gel mechanism, it is assumed that the introduction of any effective sacrificial bonds will reinforce the material. Various kinds of sacrificial bonds are attempting to induce into the hydrogel but no obvious improvement in mechanical strength has been observed [75-78]. One successful approach was recently found to fabricate strong DN gels from PAMPS powder precursors that were obtained by grinding the dried bulk PAMPS hydrogels. The so-called P-DN hydrogels containing PAMPS particles in the PAAm matrix exhibited comparable strength and toughness with those of standard DN gels [44]. The result suggests that the polyelectrolyte particles may also serve as the

sacrificial bonds to reinforce the gel. The P-DN hydrogels from grinded PAMPS particles, however, possess a rough appearance and poor reproducibility. It is also unpromising for the study of the fracture process due to the irregular shape and a wide size distribution.

A hydrogel named as microgel-reinforced (MR) hydrogel with two-phase composite structure has been developed by authors' group, where the continuous phase is a loosely cross-linked polyacrylamide (PAAm) matrix and the disperse phase is virtually double-network (DN) microgels. The MR hydrogel was prepared from a microgel particle (microgel particle was prepared by SPG membrane emulsification and UV polymerization from an aqueous phase of a ionic monomer, 2-Acrylamido-2-methylpropanesulfonic sodium:NaAMPS) in which the microgel swelled in a 2nd neutral monomer solution of acrylamide (AAm) followed by UV polymerization [38]. To further enhance the toughness, the synthesised MR hydrogel (named as sMR) was brought to apply the double network principle to introduce another polymer network of the identical 2nd neutral monomer AAm. This resulting hydrogel exhibited dramatic enhancement in mechanical strength and toughness, in comparison to the hydrogels with no microgels. MR hydrogels showed the comparable mechanical properties with the conventional bicontinuous DN hydrogels [38].

As shown in **Figure 10**, the MR gel film was capable of subjecting to dramatic elongation (**Figure 10a**) and torsion (**Figure 10b**), exhibiting extraordinary ductility and flexibility. **Figure 10c** shows the tensile stress–strain curves of sMR and MR gels. The behavior of the PAAm gel, prepared by the same two-step sequential network formation of PAAm without adding microgels, was used for comparison (shown in **Figure 10c**). The PAAm gel was very soft and ductile (modulus E, fracture stress σ_b, and fracture strain ε_b were 0.03 MPa, 0.4 MPa, and 1000%, respectively). In contrast, MR gel exhibited high E, σ_b, and ε_b up to 0.22 MPa, 2.5 MPa, and 1300%, respectively. The reinforcement efficiency (the ratio

of σ_b of MR to that of the PAAm gel) reached up to 6 times that showed the same order of magnitude as CB-reinforced vulcanizates [79]. On one hand, the increase in E is expected due to the addition of the relatively rigid microgels. (The E of microgels interpenetrated by PAAm networks was 0.34 MPa estimated from bulk gels with the same composition.) On the other hand, the increased E is also a result from the introduction of topologically constrained chain entanglements between penetrating chains of the matrix and those of the microgels. So the embedded microgels play a role as multifunctional physical cross-linking points, which effectively transfer energy across the matrix/microgel interface. The problem resides in the ability of the microgels to permit a much increased elongation at break, which perhaps stems from the abundant coiled PAAm chains stored compactly in the highly cross-linked microgels. However, sMR gel was very brittle, broke at the strain of 100%, which indicates that the molar ratio of the PAAm matrix to microgels is vital to fabricate MR hydrogels with high mechanical strength. To make a comparison between DN gels and MR gels, the tensile result of the DN gel film is also shown in **Figure 10c**. Comparing with the DN gel, MR gel showed a comparable σ_b and a slightly higher ε_b. However, MR gel showed a much lower initial modulus E than that of the DN gel, which is apparently due to the discontinuous distribution of the microgels (**Figure 10d**).

By visualizing the embedded microgels before, during, and after the elongation, mesoscale fractures of the microgels phase were confirmed, which should effectively blunt the crack and enhance the fracture propagation resistance. Therefore, it can be concluded that the essential reinforcement principle of MR gels roots in the sacrificial bonds effect contributed by the microgels. The reinforcement mechanism of DN gels with bicontinuous network structure has been elucidated that the rigid and brittle polyelectrolyte network serves as sacrificial bonds to increase the resistance dramatically against the crack propagation [55].

We assume that the high mechanical strength of MR gels root in the sacrificial bonds contributed by the DN microgels phase, similar to the fracture phenomenon occurred in DN bulk gels. A prominent hysteresis was found for MR gel (**Figure 11a**), the same as DN gels [28] but not for the PAAm gel. This result indicates that the irreversible structural change that is related to the rupture of covalent bonds occurred in the MR gel. In order to visualize this mesoscale fracture of MR gel clearly, the anionic PNaAMPS microgels were dyed selectively by the tetravalent cationic Alcian Blue (**Figure 11b**). When MR gel was elongated to the strain (ε) of 400%, the microgels deformed from sphere to prolate spheroid along with the stretching direction but showed a less ε than that of the bulk gel, corresponding to their higher modulus than the surrounding PAAm matrix phase (**Figure 11c**). The background color was attributed to the negative birefringence caused by the stretch orientation of the PAAm matrix, which changed with the degree of orientation [59]. Finally, the broken MR gel was reswollen in deionized water (**Figure 11d**). Comparing **Figure 11b** with **Figure 11d**, by statistically measuring the size of 100 microgels in these images, it was found that the volume expansibility of microgels was much larger than that of the gel, indicating that the enlarged size and residual anisotropy of microgels are mainly caused by the internal fracture of microgels, rather than by the permanent deformation of the outer matrix phase. Thus, the enlarged size and residual anisotropy of microgels give the convincing evidence that microgels structure was broken and they serve as sacrificial bonds to reinforce MR gels, in consistent with the result from macroscopic elongation. Furthermore, the microgels in the re-swollen gel still kept their integrity and did not break into pieces, which disproves the assumption of that the rigid network in DN gels was fractured into independent micro-"clusters" after being stretched proposed in elsewhere [28] Considering the embedded microgels as probe during or after elongation, some valuable results have been obtained in mesoscale to study the fracture mechanism on these novel MR gels. These results also

demonstrate that studying on the mesoscale fracture of microgels will bridge the gap between macroscopic mechanical properties and microscopic structure change.

4.4 Liquid crystalline DN gel

Most of the hydrogel, which was discussed above, has been synthesized applying the DN principle. Most of them possess amorphous structures at both molecular and macroscopic levels in contrast to the soft and wet gel-like bio-tissues. Recently, authors' group [39] has developed an anisotropic hydrogel with self-assembled liquid crystalline structure and the toughness was dramatically improved by forming double network (DN) structure and named as anisotropic-DN gel (A-DN). A-DN hydrogel was synthesized by Ca^{2+} ion-diffusion-induced molecular orientation and complex formation of a semi-rigid polyelectrolyte, poly(2,2′-disulfonyl-4,4′-benzidine terephthalamide) (PBDT) [80-83] and then polymerizing acrylamide (AAm; 2^{nd} network) in the previously formed PBDT gel (1^{st} network) applying DN principle [25, 39]. It is believed that the A-DN gel is formed first by the well-oriented anisotropically structured PBDT gel acting as a template, and the PAAm polymers as the second network, whose monomers diffuse into the anisotropic template of the PBDT aggregates beforehand and thereby possesses an anisotropic entangling structure as well. Considering this, **Figure 12a** presents a possible well-ordered structure of the A-DN gel.

The uni-axial tensile elongation along the axial direction, which was parallel to the diffusion direction of the Ca^{2+} ions, and the other, was the vertical direction demonstrated the anisotropic mechanical properties of the A-DN gel (**Figure 12c**). The elongation in the axial direction showed a nice J-curve and the elongation stress at fracture was much higher than that in the vertical direction. On the other hand, the elastic modulus (initial slope of the stress–strain curves) in the vertical direction (0.036 MPa) was higher than that in the axial direction (0.009 MPa). Regardless of the direction in which the gel was elongated, the gel

showed extraordinary extensibility that could reach 22 times the original length, as demonstrated in **Figure 12b**. The elongations in both directions were reversible before fracture [39]. In order to elucidate the effect of the individual single network (SN) of the first gel (PBDT SN gel) and the second gel (PAAm SN gel), two types of individual SN gels and A-DN gels in different directions was compared. The results are shown in **Figure 12d**. The SN PBDT gel that was stretched in the vertical direction had the highest elastic modulus of around 0.081 MPa. However, it fractured at a small tensile strain (70%), which indicates that the physically cross-linked PBDT gel was brittle and lacked elasticity. This should be attributed to the packing structure of the anisotropically self-assembled PBDT molecules [84]. On the other hand, the PAAm SN gel was softer than the A-DN gel, and large extensions were not reversible, probably because of the loose cross-linking. These results indicate that although the amount of PBDT is significantly lower than that of PAAm (1:99), it enhances the mechanical strength of the A-DN gel dramatically because of its well-oriented anisotropic structure. The high initial elastic modulus the A-DN gel in the vertical direction might be a result of the break in the PBDT packing; subsequently, the untwisting effect of the second flexible PAAm chains contribute to a large strain. In contrast, the A-DN gel in the axial direction can release the elastic modulus at the initial elongation by anisotropically entangling the PAAm chains, whose monomer diffused into the anisotropic template of the first PBDT structure. This indicates the gel still far from the perfect macroscopic anisotropy.

4.5 Macroscopically anisotropic hydrogel involving reversible sacrificial bond

Most conventional soft and wet hydrogels usually possess amorphous structure, in contrast with the natural bio-tissues that have well-defined hierarchy structure from molecular level to macroscopic scale. Although several hydrogels with high strength, such as slide ring (SR) [22] and tetra-PEG [23] gels, and toughness, such as nanocomposite (NC) [24] and double

network (DN) [25,26] gels, have been successfully developed, they also possess amorphous structure. Among them, DN gel exhibits high fracture toughness, which is related to the internal fracture of the brittle network, which avoids the stress concentration at the crack tip and dramatically enhances crack propagation resistance. That is, the brittle network serves as sacrificial bonds in the toughening of the DN gel [26]. However, the permanent fracture of the chemical (covalent) bonds might be a limitation of this gel in many practical applications [26,57]. So, if the brittle network is replaced by some reversible physical (noncovalent) bonds such as physical association, that damage upon loading and recovers back on unloading, these physical bonds serve as a reversible sacrificial bond.

Very recently, the authors' group has developed anisotropic hydrogel based on physical association that has macroscopic uni-domain lamellar bilayer structure of self-assembled poly(dodecyl glyceryl itaconate) (PDGI) stacked periodically in the ductile, hydrophilic polymer (polyarylamides: PAAm) matrix [41,42]. A schematic representation of this gel is shown in **Figure 13a**. At room temperature, a single PDGI bilayer is relatively rigid with a high modulus in the order of several MPa and the PAAm matrix is much softer than the bilayers, with a modulus of few kPa depending on the cross-linking density [41]. By incorporating the rigid bilayers with uni-axial pattern, the tensile strength of the PDGI/PAAm hydrogel has dramatically been enhanced. This is because, during tensile elongation, rigid bilayers dissociate into molecular states consuming huge amount of energy and recover to its original state after release of stress (**Figure 13a**). The tensile stress-strain curves of the gels are shown in **Figure 13b**. The single PAAm gel fractured at a tensile stress and strain of 38 kPa and 11 m/m, respectively. Surprisingly, the fracture stress (~600 kPa) and strain (~22 m/m) of the PDGI/PAAm gel that has uni-axial bilayer structure are dramatically improved with exhibiting a clear yielding at low strain of the stress-strain curve. In contrast, the

PDGI/PAAm gel that has no bilayer structure shows a stress-strain curve without yielding similar to that of the PAAm gel, only with a slight increase in the modulus and fracture stress. So, the large enhancement of the tensile strength of the gel is attributed to the uni-domain bilayer structure inside the polymer network. The bialyers serve as reversible sacrificial bonds that give rise to the excellent mechanical performances of the gel such as hysteresis, self-recovery, persistent fatigue resistance, and crack blunting [42].

Due to perfect uni-axial alignment of bilayer in the PAAm polymer matrix with stratified orientation of soft and hard layer, PDGI/PAAm hydrogel exhibited perfect anisotropy in elastic modulus. The elastic modulus parallel ($E_{\parallel}$) and perpendicular ($E_{\perp}$) to the bilayers of the gel are plotted against the DGI concentration in **Figure 13c**. The original PAAm gel possessed an isotropic elastic modulus ($E_{\parallel} \cong E_{\perp}$). However, by adding DGI, a sharp rise in $E_{\parallel}$ could be observed, whereas $E_{\perp}$ did not change significantly. The dramatic increase in $E_{\parallel}$ led to anisotropy in the elastic modulus, with the value in the direction parallel to the lamellar layers being one order of magnitude higher than that in the perpendicular direction. As the PDGI lamellar bilayers became uniformly aligned in a single direction, the initial modulus perpendicular to the lamellar layers arose primarily from the very low modulus of PAAm network, whereas that parallel to the lamellar layers arose from both the PAAm network and rigid PDGI bilayers, which has a very high modulus.

The perfect unidirectional orientation of the PDGI lamellar bilayers caused the PDGI/PAAm gel to exhibit excellent visible colors and hence an excellent color tuning property under mechanical stimuli. This color change was reversible, *i.e*., the gel changed its color under an applied mechanical stress/strain and then returned to its initial color after the removal of the stress/strain [41,42]. However, once the color changed by applying mechanical stimuli, the gel takes relatively longer time (5 to 30 min) to regain the original

color after releasing the mechanical stimuli [41,42]. The authors' group has dramatically improved the mechanical response (< 15s) of the PDGI/PAAm gel by applying double network principle [85].

5. Biological application

5.1 A replacement of artificial cartilage

The normal cartilage tissue highly contributes to the normal joint functions involving ultra-low friction, distribution of loads, and absorption of impact energy. The cartilage tissue is occasionally injured in athletic activities, and frequently becomes degenerated by aging. Partial or complete loss of cartilage tissues leads to future problems of the knee joint, such as osteoarthrosis. When the normal cartilage tissue is damaged, it is extremely difficult to regenerate these tissues with currently available therapeutic treatments. Therefore, it is important to develop substitutes for the normal cartilage tissue as a potential therapeutic option. Potential materials for the artificial cartilage are required to be viscoelastic, strong, durable to repetitive stress, low in friction, resistant to wear, resistant to biodegradation, and regeneration within the living body. In the following section, the applicability of the DN gels, which synthesized by our group, as a potential cartilage material are discussed.

5.1.1 Resistance against wear

Yasuda's group has tested four novel DN hydrogels developed in Gong's group for biological application, for example as a cartilage tissue. The samples involve PAMPS/PAAm DN gel which consists of poly(2-acrylamide-2-metyl-propane sulfonic acid) and polyacrylamide, PAMPS/PDAAAm gel which consists of poly(2-acrylamide-2-metyl-propane sulfonic acid) and poly(N,N′-dimetyl acrylamide), cellulose/PDMAAm gel which consists of bacterial cellulose and poly(N,N'-dimetylacrylamide), and cellulose/gelatin gel which consists of

bacterial cellulose and gelatin. On pin-on-wear flat testing, PAMPS/PDMAAm DN gel has exhibited an amazing wear property as a hydrogel that is comparable to the ultra-high molecular weight polyethylene, which was used as a control of a clinically available material, whereas the PAMPS/PAAm gel, cellulose/PDMAAm gel, and cellulose/gelatin gel have shown weak resistance against the wear [86,87]. Therefore, the PAMPS/PDMAAm DN gel might be the most promising material for artificial cartilage for further evaluations from various viewpoints.

5.1.2 Implantation of DN gel specimens into the subcutaneous tissue

The biodegradation and the biological reaction of the PAMPS/PDMAAm DN gel were evaluated after implantation into a subcutaneous tissue. The PAMPS/PDMAAm DN gel specimens ($10 \times 10 \times 5$ mm^3) were implanted into the subcutaneous tissue, according to the guideline for biological evaluation of the safety of biomaterials, which had been published by the Ministry of Health, Labour and Welfare, Japan [88,89]. A total of six mature female Japanese white rabbits (3.3 ± 0.3 kg) were used and the experiments were carried out in the Institute of Animal Experimentation, Hokkaido University School of Medicine under the Rules and Regulation of the Animal Care and Use Committee, Hokkaido University School of Medicine. The implanted gel specimens were carefully harvested from the subcutaneous tissue, avoiding injury of the specimens. The harvested specimens underwent mechanical testing immediately after harvest **[**86**]**. Macroscopic situations of the implanted massive gel specimens in subcutaneous tissues were observed in careful dissection. Then, the tissues surrounding the gel specimens were histologically examined in the same manner as described elsewhere [89]. All the mechanical measurements were performed at room temperature because the mechanical properties of PAMPS/PDMAAm DN hydrogel are not different between the room temperature and the body temperature [87].

At 6 weeks after implantation, the ultimate stress and the tangent modulus of PAMPS/PDMAAm DN gel were significantly increased from 3.10 and 0.20 MPa, respectively, to 5.40 and 0.37 MPa, respectively, with a significant reduction of the water content after implantation (94 to 91%) [87]. Concerning the human knee cartilage, Athanasiou *et al.* [90] reported that the aggregate modulus averaged 0.71 MPa. The ultimate compressive stress of the tested DN hydrogels is higher than that of the above described natural cartilage. The tangent modulus of the PAMPS/PDMAAm, is comparable with that of the above described natural cartilage. The implantation tests demonstrated that, PAMPS/PDMAAm DN gel induced a mild inflammation at 1 week, and the degree of the inflammation significantly decreased at 4 and 6 weeks into the same degree as that of negative control [**Figure 14a-c**]. As mentioned previously that the PAMPS/PDMAAm DN gel has an excellent wear property in pin-on-flat-type wear testing [86], and that this gel is hardly degraded when it is implanted into a living body [87], this gel has a possibility to be a potential material that may meet the requirements of artificial cartilage in the future.

The *in vivo* influence of a PAMPS/PDMAAm DN hydrogel on counterface cartilage in rabbit knee joints and its *ex vivo* friction properties on normal cartilage were evaluated. In the *in vivo* experiment, the DN gel was implanted in a surgically created defect in the femoral trochlea of rabbit knee joints and the left knee was used as the control. The artificial PAMPS/PDMAAm DN gel cartilage into a femoral cartilage defect provides no significant damage not only to the opposite normal cartilage in the patella but also to the postoperative healing of the knee joint at 4 weeks after surgery (**Figure 15**). Specifically, observation with the confocal laser scanning microscopy showed that there were no statistical differences in the cartilage surface roughness and the number of the small pits, which commonly exist on the normal cartilage surface. In *ex vivo* experiment, the friction property between the normal

and the artificial cartilage was determined using a joint simulator apparatus. The mean friction coefficient of the DN gel to normal cartilage was 0.029, while that of the normal-to-normal cartilage articulation was 0.188. The coefficient of the DN gel-to-normal cartilage articulation was significantly lower than that of the normal-to-normal cartilage articulation ($p < 0.0001$) [91] This study suggested that the PAMPS/PDMAAm DN gel has very low friction coefficient on normal cartilage and has no significant detrimental effects on counterface cartilage *in vivo*, and can be a promising material to develop the artificial cartilage.

5.1.3 Spontaneous Cartilage regeneration

Yasuda *et al* has discovered that the hyaline cartilage regeneration has been induced *in vivo* in a large osteochondral defect in the rabbit at 4 weeks by implanting a PAMPS/PDMAAm DN gel plug at the bottom of the defect so that a 1.5- to 3.5-mm-deep vacant space was intentionally left in the defect [92]. This discovery proposes a novel strategy to repair an osteochondral defect in the field of joint surgery, that is, induction of cartilage regeneration in a vacant defect using artificially synthesized hydrogel without any cultured cells or mammalian-derived scaffolds.

A 4.3-mm-diameter osteochondral defect was created in rabbit trochlea. A DN gel plug was implanted into the defect of the right knee so that a defect 2 mm in depth remained after surgery. An untreated defect of the left knee provided control data. The osteochondral defects created were examined by histological and immunohistochemical evaluations, surface assessment using confocal laser scanning microscopy and real-time polymerase chain reaction (PCR) analysis at 4 and 12 weeks [93]. At 4 weeks, the defects treated with the DN gel were almost completely filled with a regenerated white opaque tissue (**Figure 16a**), while the defects without any treatment were insufficiently filled with white or reddish, opaque, patchy tissues (**Figure 16b**). In the latter defects, the defect margin was mostly visible, and

the surface appeared to be irregular. At 12 weeks, the defects treated with the DN gel were almost completely filled with a white opaque tissue (**Figure 16c**), and we did not find any obvious differences in gross appearance compared with the 4-week observations. In contrast, the defects without any treatment were poorly filled with a reddish, opaque, patchy tissue (**Figure 16d**). The mean surface roughness of the untreated control was significantly higher than the normal cartilage at 12 weeks ($P = 0.0106$), while there was no statistical difference between the DN gel–implanted and normal knees. Finally, it is feasible to achieve articular cartilage repair using a special and novel DN gel without including cells, using the mature rabbit femoral trochlea osteochondral defect model over a 12-week period [93]. This method appears to generate an excellent hyaline cartilage repair without the use of exogenous cells and without fully filling the osteochondral defect. This novel gel strategy needs to be further validated in a larger animal model to determine its efficacy for possible use in the human.

5.2 Cornea repair material

Frank's group has applied the poly(ethylene glycol)/poly(acrylic acid) (PEG/PAAc) IPN hydrogel as cornea repair materials. They have found that PEG/PAAc gel had a glucose diffusion coefficient nearly identical to that of the human cornea (~2.5×10^{-6} cm^2/sec). While implanted intrastromally in rabbit corneas, this transparent hydrogel was retained and well-tolerated for a period of 14 days [94]. The retained hydrogels stayed optically clear and the epithelium remained intact and multilayered, indicating that the material facilitated glucose transport from the aqueous humor to the anterior part of the eye. The results from these experiments indicate that PEG/PAAc hydrogels are promising candidates for corneal implant applications such as keratoprostheses and intracorneal lenses.

6. Conclusions and future scope

The double-network (DN) hydrogel, which generally composed of a rigid and brittle first network and a soft and ductile second network, exhibits high fracture stress and toughness much larger than that of the individual single-network hydrogels but similar to that of rubber and load-bearing soft tissues. Inspired with the DN concept, the authors' group as well as other groups has also developed some novel systems such as cellulose based anisotropic DN gel [35,36], void-DN gel [37], microgel-reinforced particle DN gel [38], liquid crystalline DN gel [39,41,42], poly(ethylene glycol)-diacrylate/poly(acrylic acid) (PEG-DA/PAAc) inverse DN gel [45,46], the modified hyaluronan/poly(N,N'-dimethylacrylamide) (PHA/PDMAAm) [47], poly(ether-urethane)/poly(methyl-methacrylate) (PEU/PMMA) [48] DN gels. These entire DN gel systems exhibit enhanced mechanical strength and toughness much better than that of the individual components and some of them possess fracture stress and toughness in the order similar to the soft bio-tissues. The enhancement of a single network gel based on DN structure would substantially expand the application of DN gels in both medical and industrial fields. To be specific, cellulose based DN gel and liquid crystalline DN gel exhibit anisotropic mechanical property which is highly important for anisotropic functioning in the living organism. On the other hand, void-DN gel and microgel-reinforced particle DN gel not only reinforced the mechanical strength and toughness but also allowed a deep understanding of the mesoscale fracture mechanism of DN structure. Notably, PAMPS/PDMAAm DN gel possesses extremely low friction [91] and strong resistance against wear [86]. After implanting in a living body (rabbit), the gel is hardly degraded [87], induced negligible inflammation [89], and spontaneously generated an excellent articular/hyaline cartilage repair without the use of exogenous cells and without fully filling the osteochondral defect [92,93]. The novel gel strategy needs to be further validated in a larger animal model to determine its efficacy for possible use in the human.

It should be noted here that the DN gel might have a weak fatigue resistance, which will be a limitation in many practical applications. This limitation originates from the fact that the toughening is due to the irreversible failure of covalent bonds in the first network [26,55,57,58,60]. However, the DN gel concepts can, in principle, be applied to other self-healing types of materials [95-98], if the covalent bonds are replaced by reversible bonds. The challenge is to obtain bonds that are both strong and reversible. Recently, authors' group has developed a macroscale anisotropic hydrogel that has membrane-like lamellar bilayer structure with unidirectional alignment [41]. This gel showed excellent toughness, self-recovery and fatigue resistance [42].

Recent studies show that DN gels have good biocompatibility and are good scaffold for cell cultured on the surface. However, developing tough scaffold for 3-dimensional cell culture is also necessary since it can mimic some cell growth in typical environment, such as the chondrocyte in biological cartilage. Furthermore, it should be good to implant the artificial tissues cultured with cells in body to help the repair and regeneration of living organs.

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Abbreviations

DN	double network
IPN	interpenetrating polymer networks
PAMPS	poly(2-acrylamido-2-methylpropanesulfonic acid)
PAAm	polyacrylamide
BC	bacterial cellulose
PBDT	poly(2,2′-disulfonyl-4,4′-benzidine terephthalamide)
MR	microgel-reinforced
sMR	single network microgel-reinforced
A-DN	anisotropic double network
PEG	poly(ethylene glycol)
PAAc	poly(acrylic acid)
PEU	poly(ether-urethane)
PMMA	poly(methyl-methacrylate)
PHA	poly (hyaluronan)
PDMAAm	poly(N,N'-dimethylacrylamide)
JF	jellyfish
MPa	megapascal
ε	strain
σ	stress
E	elastic modulus
T	tearing energy

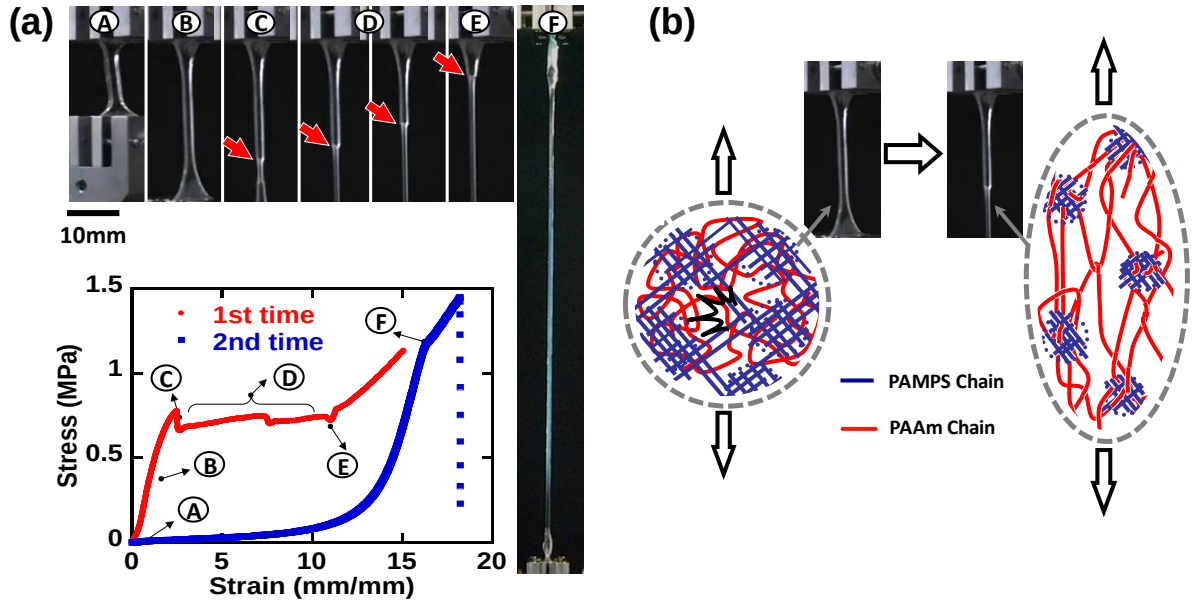

Figure 1: (a) Loading curves of PAMPS/PAAm double network (DN) gel under uniaxial elongation at a rate of 0.13 s^{-1}, and images demonstrating the necking process. The insert letters represent the correspondence between the images and the date points in the loading curves. (b) Illustration of the network structure of the DN gel before and after necking. Above a critical stress, PAMPS network fractures into clusters that behave as a sliding cross-linker of PAAm. After necking DN gel becomes soft. Reproduced with permission from the literature [26]

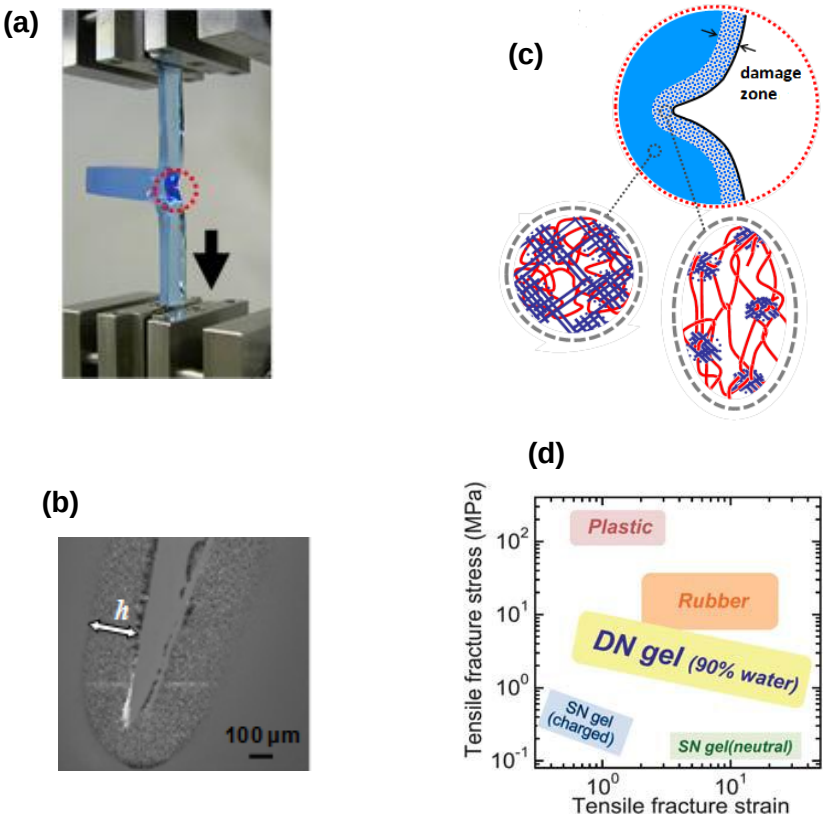

Figure 2: (a) Image of the tearing test of double network (DN) gel. (b) Image of the crack tip of the DN gel after tearing observed under a color three-dimensional violet laser scanning microscope. (c) Illustration of network structure of the DN gel at the crack front and damage zone. (d) Comparison of the toughness of the DN gel with various polymer materials. Reproduced with permission from the literature [26,55]

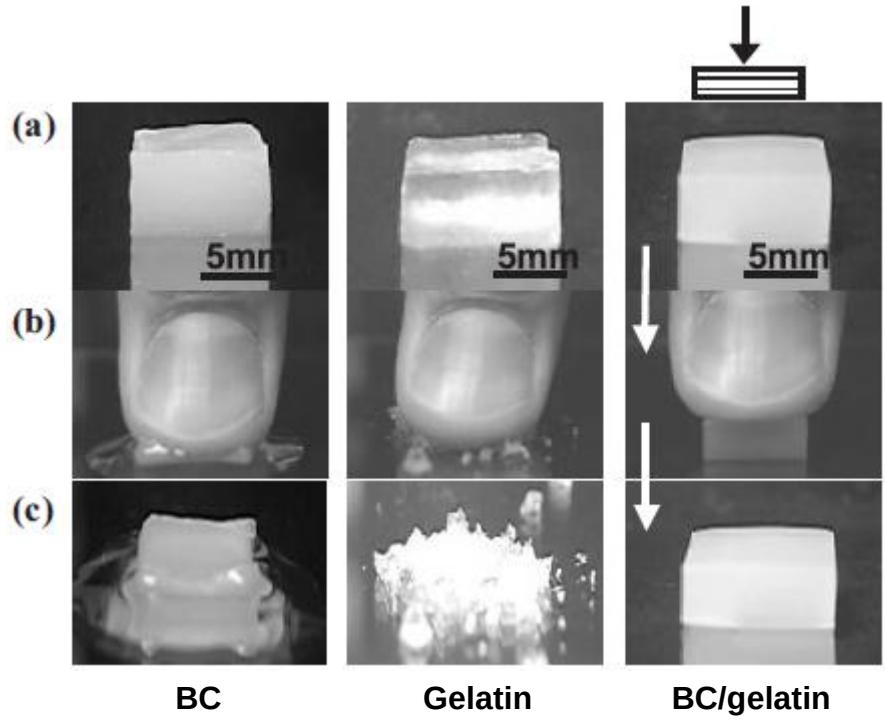

Figure 3: Photographs of the bacterial cellulose (BC), gelatin, and BC/gelatin DN gels taken (a) before compression, (b) during compression, and (c) after 10 min. compression. Reproduced with permission from the literature [35]

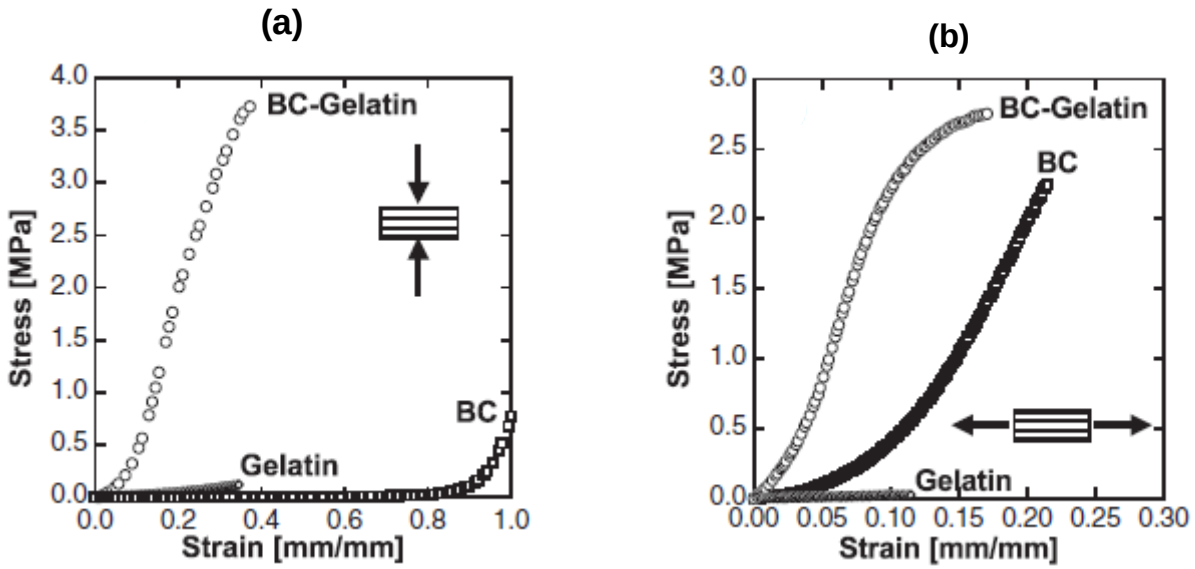

Figure 4: Compressive (a) and tensile (b) stress-strain curves of bacterial cellulose (BC), gelatin, BC/gelatin DN gels. The compression and elongation were performed in perpendicular to and along with the stratified direction of BC and BC/gelatin DN gels, respectively. Concentration of gelatin in feed: 30w%. EDC concentration: 1M. Reproduced with permission from the literature [35]

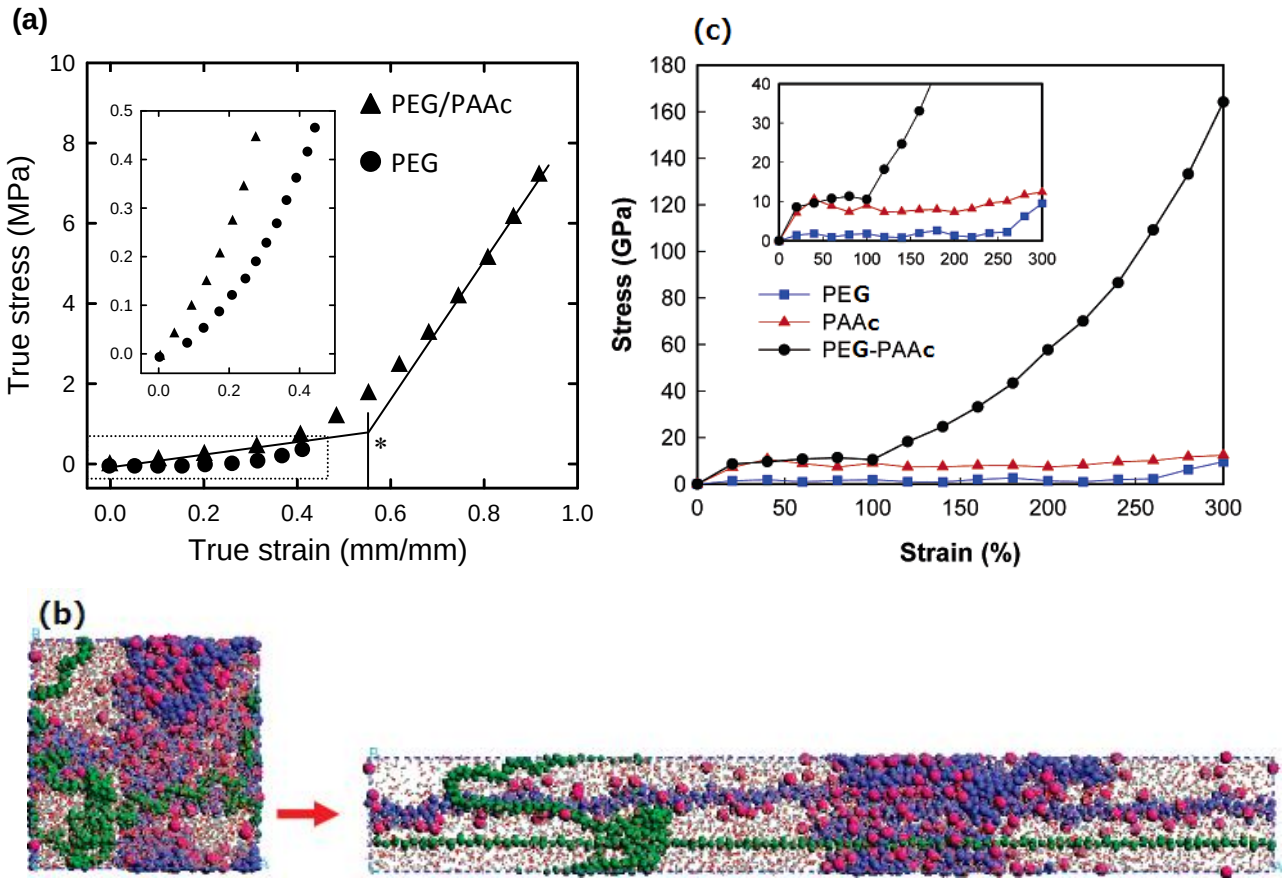

Figure 5: (a) True compressive stress versus true strain plots for (a) PEG single network gel and (b) PEG/PAAc DN gel. The molecular weight of PEG is 4600 Da in both gels. The intersection (*) between the initial and final tangents to the stress-strain curve of PEG/PAAc defines the critical strain (ε_{crit}) for strain hardening in each IPN. (b) Molecular dynamic simulations of PEG/PAAc DN hydrogel system at normal state and elongated state (300%). (c) Stress-strain curves of PEG, PAAc, and PEG/PAAc hydrogels from uni-axial elongation simulations. Reproduced with permission from the literature [45, 47]

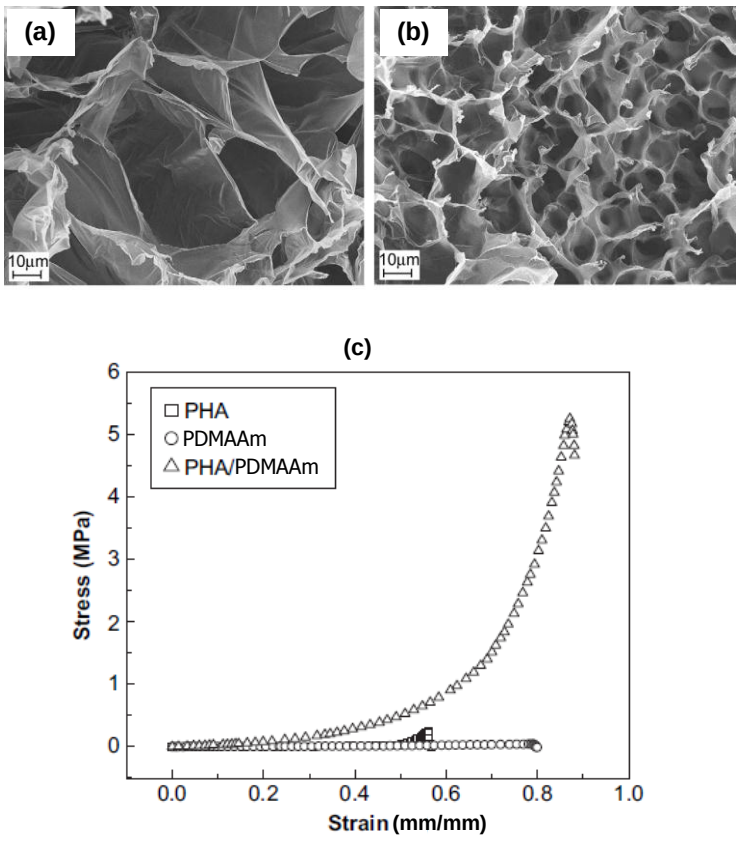

Figure 6: Representative SEM images for the (a) PHA and (b) PHA/ PDMAAm. (c) Stress-strain profiles for the PHA, PDMAAm, and PHA/PDMAAm hydrogels under uniaxial compression. Reproduced with permission from the literature [50]

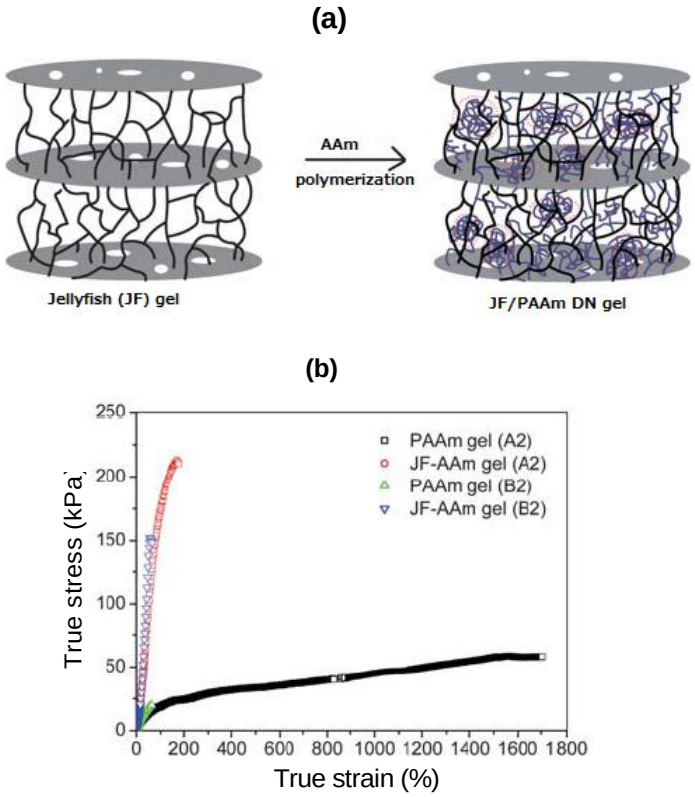

Figure 7: (a) Schematic microstructures of jellyfish (JF) gel and JF/PAAm DN gel. (b) The typical tensile stress–strain curves of JF/PAAm and PAAm gels. Reproduced by permission of the *Royal Society of Chemistry* [51]

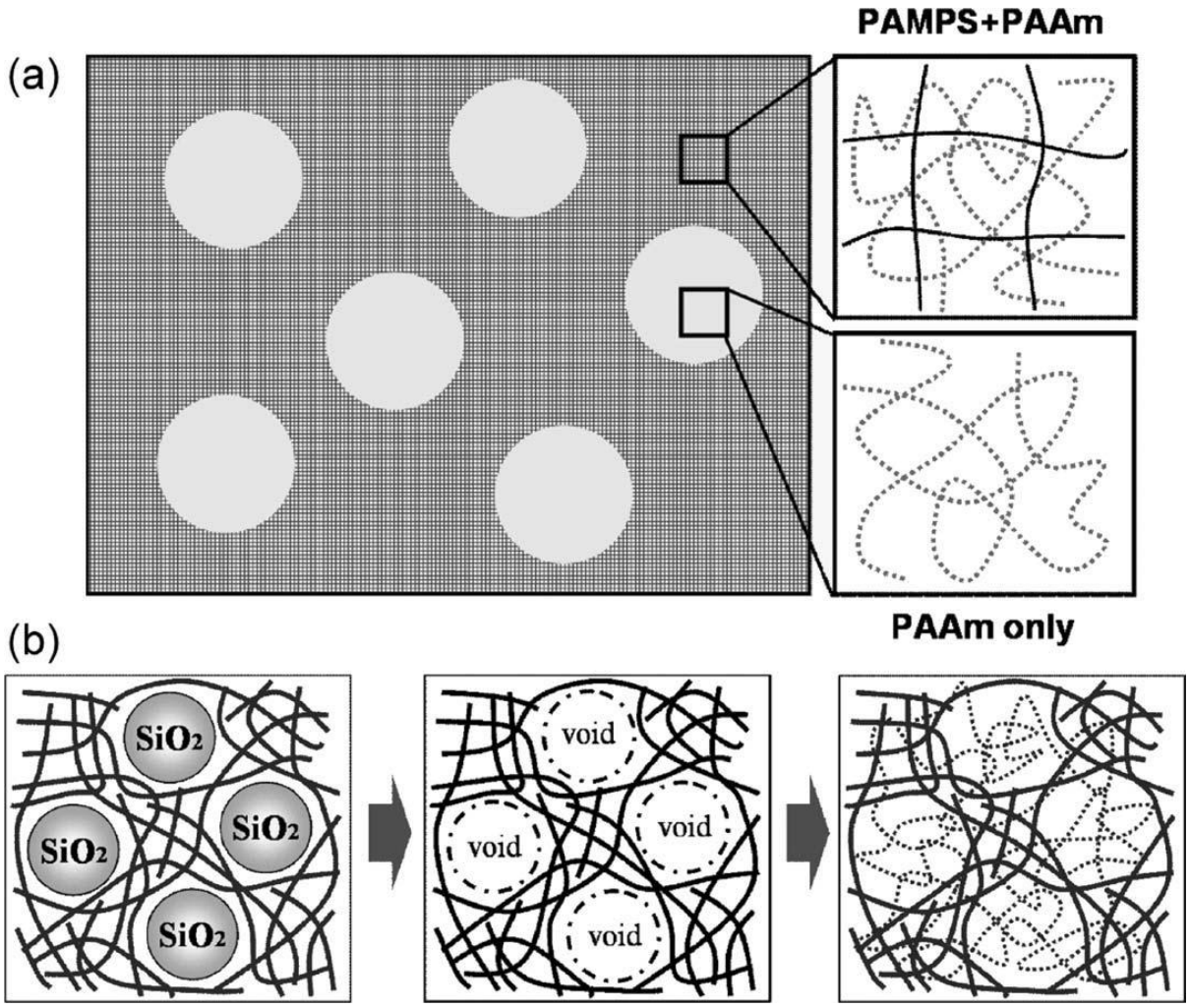

Figure 8: (a) The structure model and (b) the synthesizing pathway of void-DN gels with hard PAMPS/PAAm body and soft spherical PAAm void, which are obtained by polymerizing PAAm (dotted chain) in the presence of PAMPS gels (solid chain) containing hollow spherical structure. Reproduced with permission from the literature [37]

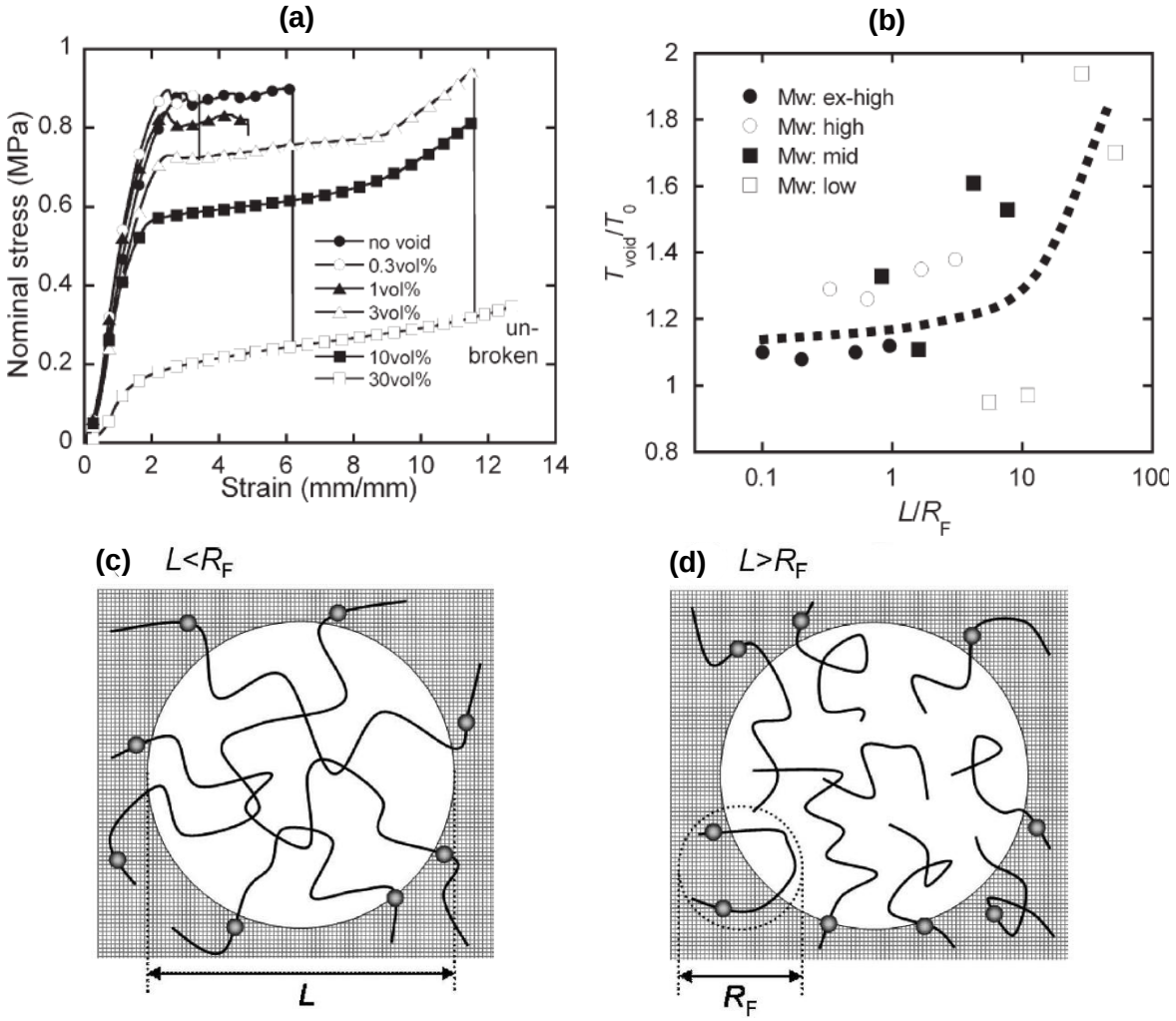

Figure 9: (a) Stress–strain curves of void-DN gels with various volume fraction of the void (void diameter, L = 200 nm). The initiator concentration of the second network was 0.02 mol % and M_w was 3.0 × 10^6 g/mol. The tensile velocity was 100 mm/min. (b) Relative tearing energy (T_{void}/T_0) dependence on L/R_F (R_F: Flory radius of the PAAm). T_{void}/T_0 increased twice when the void diameter L was much larger than R_F (A line is guide for eyes). T_{void} and T_0 is the tearing energy of the void and void-free DN gel, respectively. (c) In the case of $L < R_F$, the void is bridged by several PAAm chains via the covalent bonds between the two networks. (d) If $L>R_F$, PAAm chains are relatively too short to bridge the void structure, thus, the void can form ‘‘true’’ hollow structure. The mesh around the void denotes PAMPS network and the solid chains denote PAAm. Reproduced with permission from the literature [37]

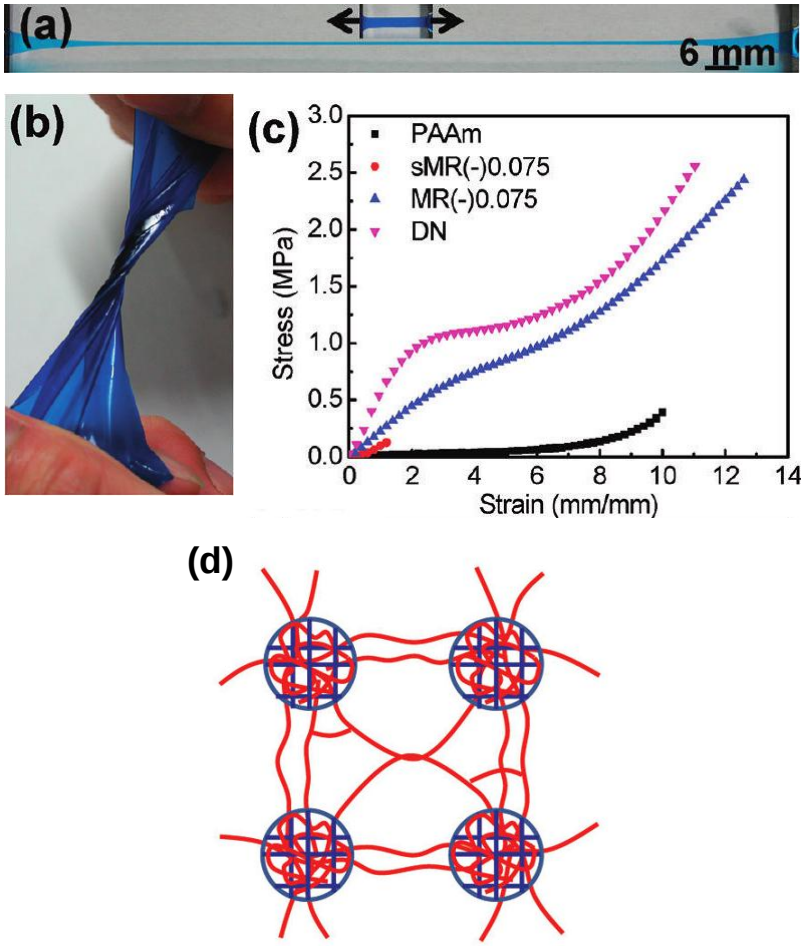

Figure 10: Microgel reinforced particle double network gel (MR gel) film, dyed by Alcian Blue, subject to high elongation from the free-standing state to the stretching state of strain = 11mm/mm (a) and torsion (b). (c) Comparison of tensile stress-strain curves of PAAm, sMR, MR, and conventional DN gels. (d) Schematic representation of the network structure of MR gel. Reproduced with permission from the literature [38]

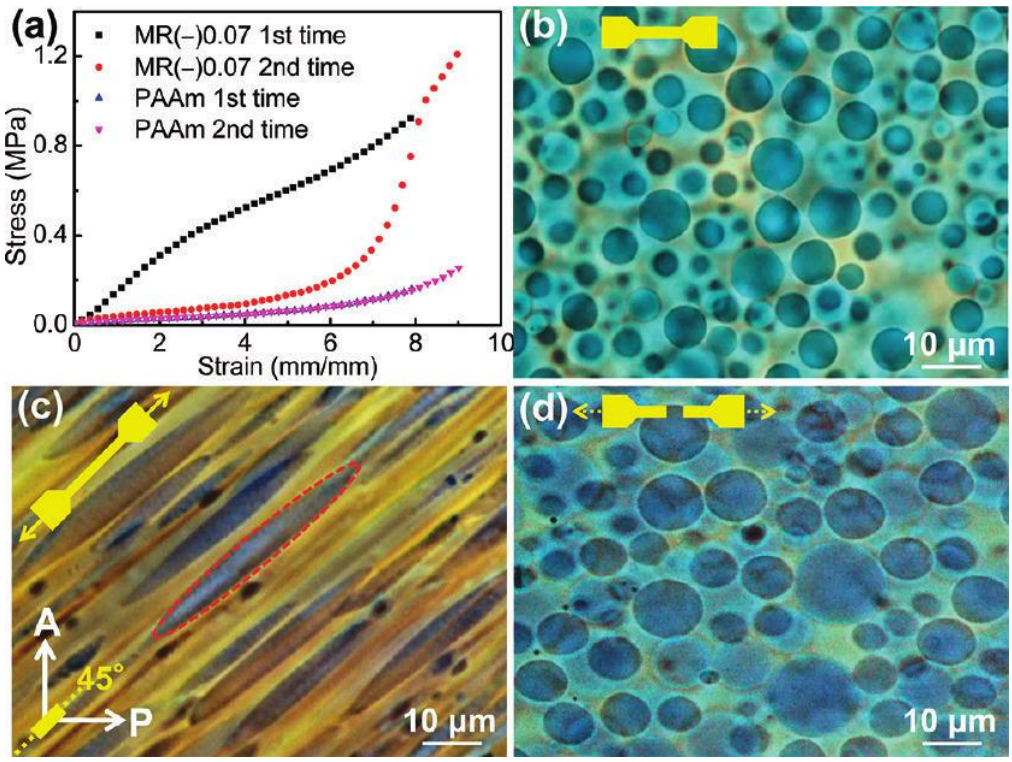

Figure 11: (a) Hysteresis in stress-strain curves of microgel reinforced particle double network gel (MR gel) and the PAAm gel. The first and the second elongation are stopped at the strain = 8 mm/mm and strain = 9 mm/mm, respectively. (b) Optical microscopy image of MR gel film at the free-standing state. (c) Real-time tensile observation of MR gel film at the strain of 4 mm/mm by a polarizing microscope, equipped with the crossed polarizers and the 530 nm tint plate. The sample was stretched 45° against the polarizers. The red dashed line indicates the deformed microgel. (d) Residual strain observation of re-swollen MR gel film after tensile fracture by an optical microscope. The elliptic shape of the micogels indicates the occurrence of the internal fracture after elongation. MR gel film is dyed by Alcian Blue for (b–d). Reproduced with permission from the literature [38]

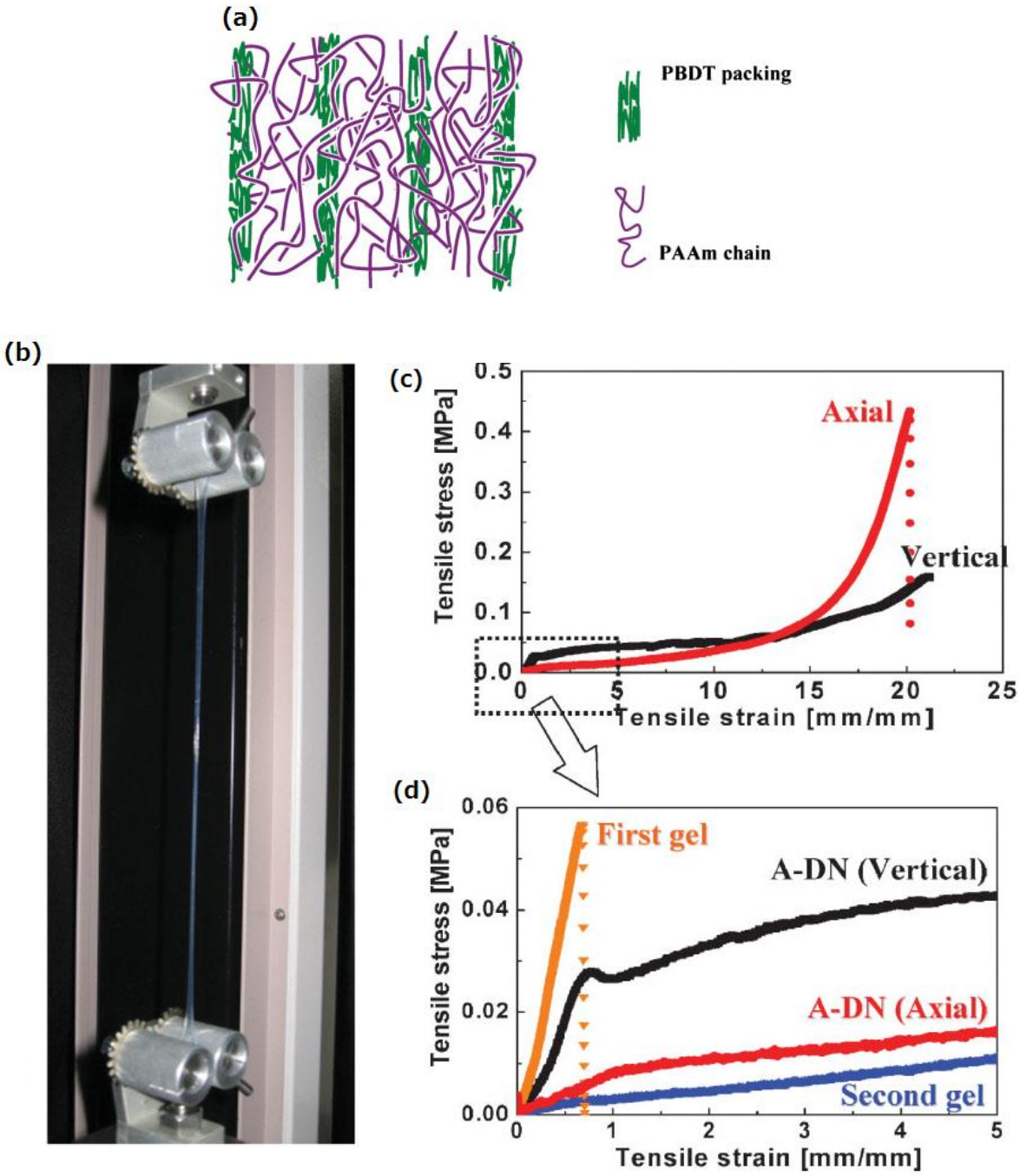

Figure 12: (a) Schematic representation of a possible well-ordered structure in the anisotropic double network (A-DN) gel. High extensibility of the A-DN gel containing 1wt % PBDT: (b) Photograph demonstrating the tensile capability of the A-DN gel that can elongate to over 22 times of its original length. (c) Tensile stress–strain curves of A-DN gel in axial and vertical directions. (d) Enlarged curves at the initial elongation of the A-DN gel and corresponding two individual single network gels (PBDT SN gel and PAAm SN gel). Reproduced with permission from the literature [39]

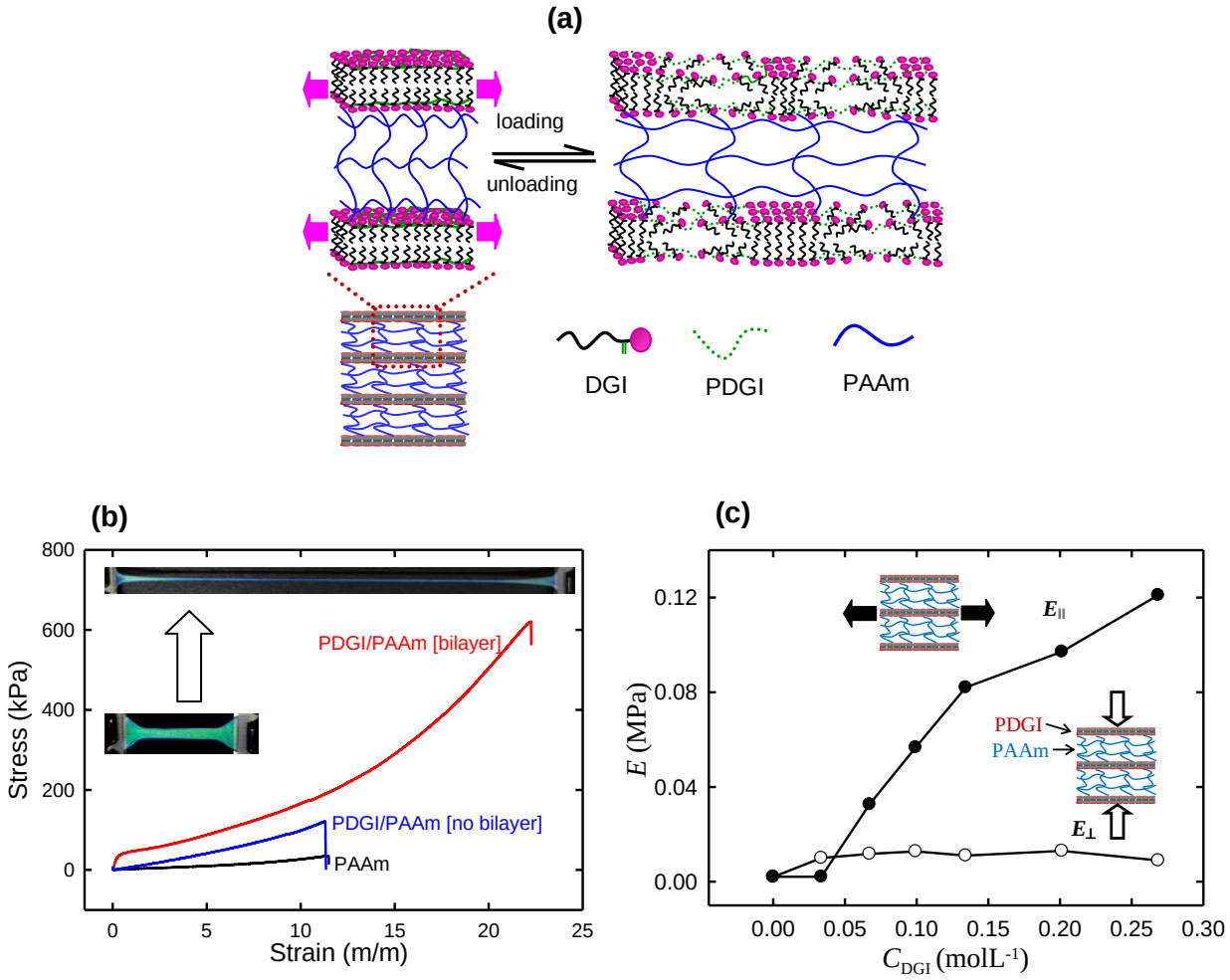

Figure 13. (a) An illustration of the stratified structure of PDGI/PAAm hydrogel consists of PDGI lamellar bilayers and PAAm matrix, and the fracture process of the bilayers on uniaxial elongation in the direction parallel to the bilayers. (b) Nominal stress as a function of strain at a stretching velocity of 200 mm/min for the PAAm gel, PDGI/PAAm gel with and without lamellar bilayer structure. The tensile deformation was performed along the lamellar bilayers direction as indicated by the illustration (a) and inserted images (b). (c) DGI concentration dependence of overall elastic modulus of PDGI/PAAm gels in parallel to lamellar layers (●, $E_{\parallel}$) and perpendicular to lamellar layers (○, $E_{\perp}$). Reproduced with permission from the literature [41,42]

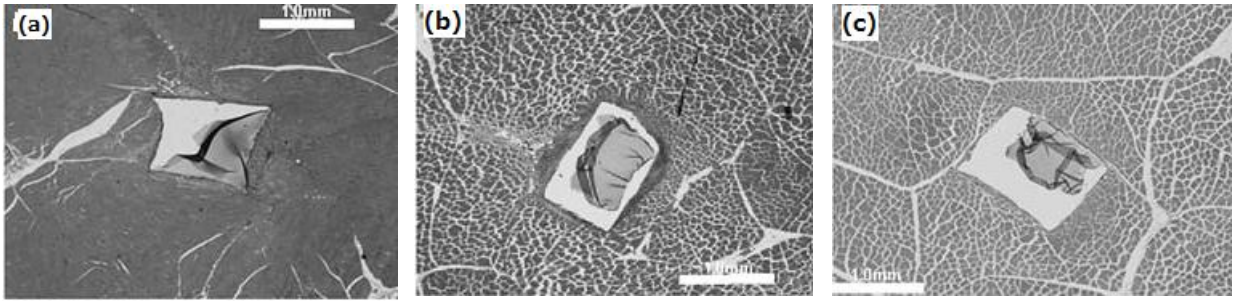

Figure 14: Histological observations of PAMPS/PDMAAm DN gel at 1 (a), 4 (b), and 6 (c) weeks. Reproduced with permission from the literature [89]

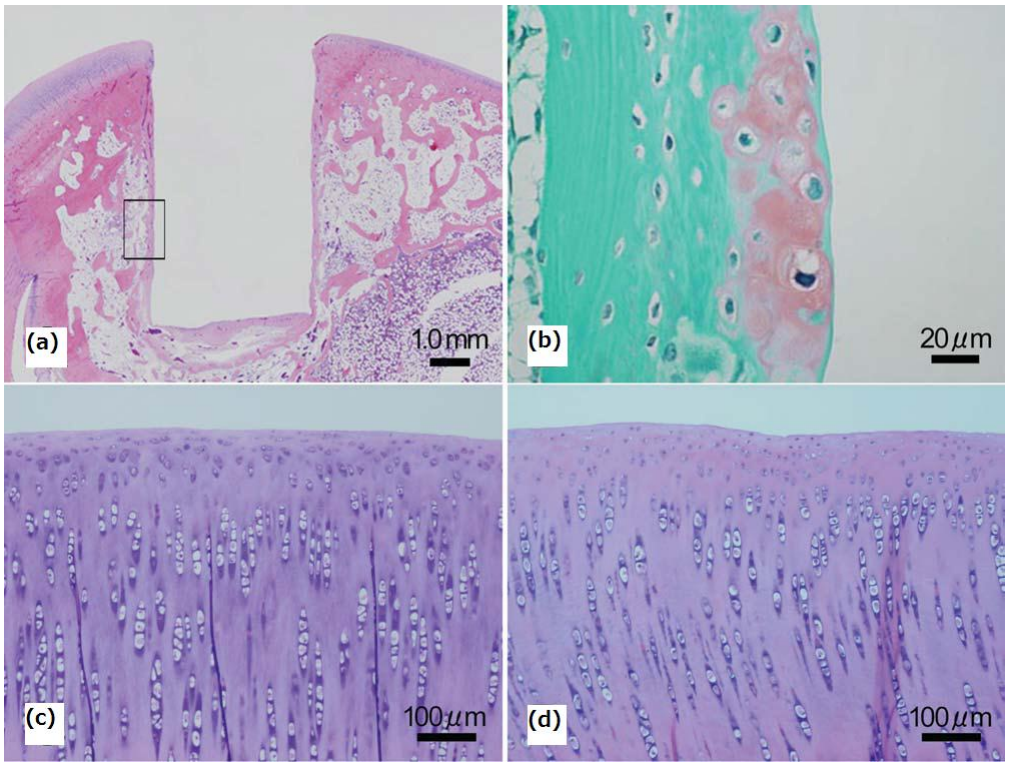

Figure 15. Histological and immunohistochemical evaluations at 4 weeks. The double network (DN) gel implanted defect was surrounded by the fibrous and bone tissues (a: HE, ×2). The DN gel was in place at the time of sacrifice. Some small areas stained with Safranin-O was found at the interface between the DN gel and the bone tissues (b: Safranin-O, ×20). The patella of both the sham-operated and the DN gel implanted knees demonstrated almost normal appearance at 4 weeks (HE, ×10, c: sham-operated knee, d: DN gel implanted knee). Reproduced with permission from the literature [91]

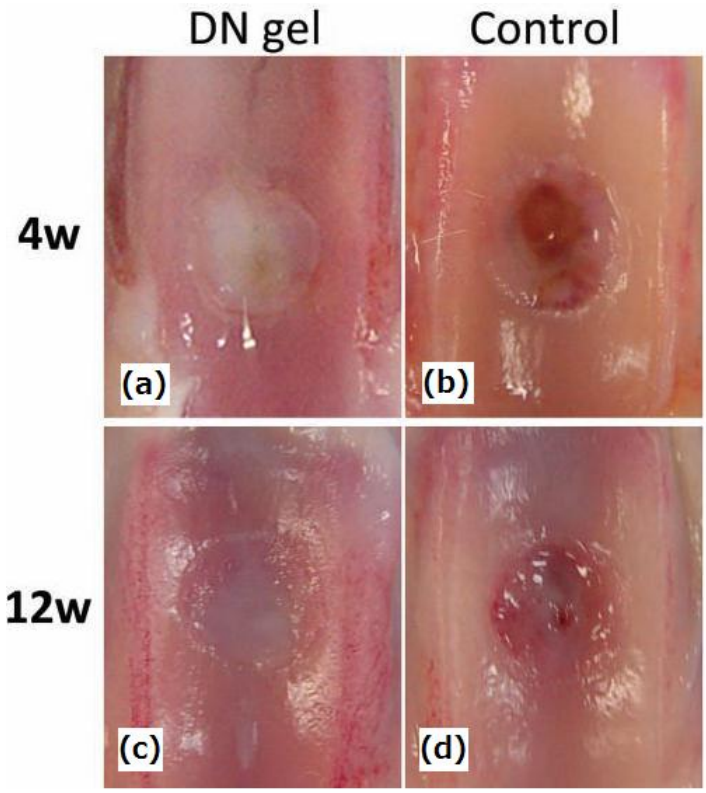

Figure 16. Gross observations of the joint surface. (a) Double network (DN) gel implanted specimen at 4 weeks. (b) Untreated control at 4 weeks. (c) DN gel implanted specimen at 12 weeks. (d) Untreated control at 12 weeks. The defects treated with the DN gel were almost completely filled with a white opaque tissue at 12 weeks (c), and it was not observed any obvious differences in gross appearance compared with the 4-week observations (a). Reproduced with permission from the literature [93]

Graphical Abstract

Super tough double network hydrogels and their application as biomaterials

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[a]Faculty of Advanced Life Science, Hokkaido University, Sapporo 060-0810, Japan

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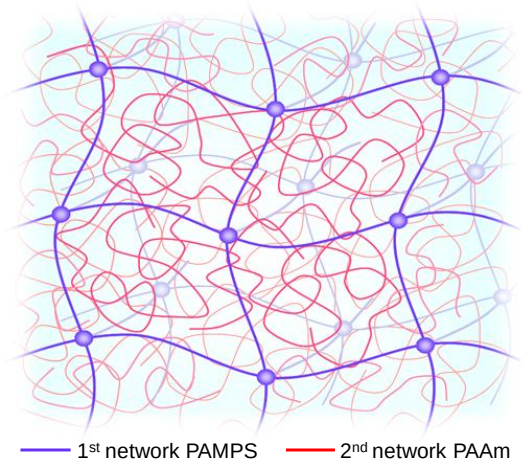

Authors' Profile

Md. Anamul Haque

Md. Anamul Haque graduated in Master of Science from University of Dhaka, Bangladesh in 2008. He achieved the PhD degree from Hokkaido University, Japan in 2011. During doctoral research, he has carried the research on the creation of an anisotropic hydrogel with well define hierarchical structure. Now he is concentrating on high functionalization of the anisotropic hydrogel such as role of sacrificial bond on toughness, multi stimuli color sensor.

Takayuki kurokawa

Takayuki Kurokawa graduated in polymer science from Hokkaido University, Japan in 2000. He received his PhD for study on Effect of Polymer Dynamics on Friction of Gels from Hokkaido University in 2005. He joined RIKEN, Japan as a postdoctoral researcher, then Creative Research Institution at Hokkaido University as an assistant professor since 2009. He focuses on functions of polymer gels, such as mechanical property, permeability, and biological property.

Jian Ping Gong

Jian Ping Gong is the professor of Faculty of Advanced Life Science, Hokkaido University. She gained her Doctor of Engineering from Tokyo Institute of Technology and joined the faculty at the Hokkaido University in 1993. She received Wiley Polymer Science Award (2001), The Award of the Society of Polymer Science Japan (2006), and the Chemical Society of Japan Award (2011). She serves on the editorial and advisory boards of Soft Matter, Macromolecules, Biointerphases, and Asia Materials. Gong is currently concentrating on the researches of novel hydrogels with high mechanical performances and its application as biomaterials.