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Hybrid Hydrogels with Extremely High Stiffness and Toughness

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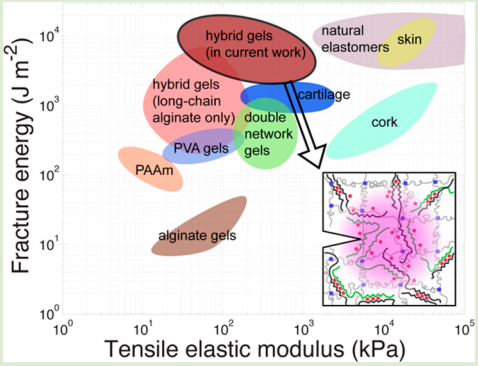
Supporting Information

ABSTRACT: The development of hydrogels for cartilage replacement and soft robotics has highlighted a challenge: load-bearing hydrogels need to be both stiff and tough. Several approaches have been reported to improve the toughness of hydrogels, but simultaneously achieving high stiffness and toughness remains difficult. Here we report that alginate-polyacrylamide hydrogels can simultaneously achieve high stiffness and toughness. We combine short- and long-chain alginates to reduce the viscosity of pregel solutions and synthesize homogeneous hydrogels of high ionic cross-link density. The resulting hydrogels can have elastic moduli of ~1 MPa and fracture energies of ~4 kJ m^{-2}. Furthermore, this approach breaks the inverse relation between stiffness and toughness: while maintaining constant elastic moduli, these hydrogels can achieve fracture energies up to ~16 kJ m^{-2}. These stiff and tough hydrogels hold promise for further development as load-bearing materials.



Hydrogels are used as scaffolds in tissue engineering,[1] carriers for drug delivery,[2] valves in microfluidics,[3] and superabsorbent polymers in disposable diapers.[4] Many other applications require hydrogels of exceptional mechanical properties. Examples include biomedical applications such as materials for cartilage replacement,[5] engineering applications such as swellable packers for oil and gas recovery,[6] and artificial muscles and artificial nerves in the nascent field of soft machines.[7−9] These load-bearing applications of hydrogels are often limited by low stiffness and toughness.[10] Hydrogels for cartilage replacement, for instance, require high stiffness and toughness to retain shape and to resist fracture, respectively.[5] Several approaches have been reported to improve the toughness of hydrogels,[11−18] but simultaneously achieving high stiffness and toughness remains a challenge. Stiffness and toughness of polymer networks are often inversely related. According to the Lake−Thomas model, for example, as the cross-link density decreases, toughness increases, but stiffness decreases.[19] Most hydrogels are either stiff and brittle with low fracture energies on the order of 10 J m^{-2} or tough and compliant with low elastic moduli on the order of 10 kPa. To place these values in context, note that cartilage has elastic moduli on the order of 1000 kPa and fracture energies on the order of 1000 J m^{-2}.[20,21]

It has been discovered that hydrogels can achieve high toughness by using double networks.[11,22] A recent work has shown that alginate-polyacrylamide hydrogels can achieve fracture energy of 9000 J m^{-2}.[13] Tests of biocompatibility have shown that alginate-polyacrylamide hydrogels have minimal effects on cells in vitro and in vivo, encouraging further exploration of the potential of these hydrogels as biomaterials.[23] For example, these hydrogels have been infused into a scaffold of woven fibers to mimic cartilage.[24] Although the alginate-polyacrylamide hydrogels have achieved exceptionally high toughness, their stiffness is modest for three reasons. First, the concentration of alginate in the hydrogel is low; any attempt to significantly raise the concentration of alginate is frustrated by the high viscosity, making it difficult to mix the ingredients to form a homogeneous hydrogel. Second, the cross-link density of alginate is low because the cross-linker, calcium sulfate, has low solubility. Third, as mentioned above, stiffness and toughness are often inversely related. As the stiffness increases, the toughness decreases significantly.

Here we report that alginate-polyacrylamide hydrogels can simultaneously achieve high stiffness and toughness. We increase the concentration of alginate while maintaining relatively low viscosity by using both short- and long-chain alginates. We increase the cross-link density of alginate while maintaining homogeneous distribution of alginate by using a combination of calcium sulfate and calcium chloride as cross-linkers. This approach breaks the inverse relation between stiffness and toughness. The resulting hydrogels achieve stiffness and toughness significantly beyond those of existing hydrogels (Figure 1).

An alginate-polyacrylamide hydrogel consists of two interpenetrating polymer networks. Polyacrylamide forms a covalently cross-linked network (Figure 2a). Alginate is a linear block copolymer of 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues.[25] This block copolymer forms cross-links via ionic interactions between the G residues on the chains and chelating ions such as Ca^{2+} (Figure 2b).[26,27] The high toughness results from the synergy of two mechanisms: crack bridging by the covalently cross-linked polyacrylamide network and energy dissipation by unzipping

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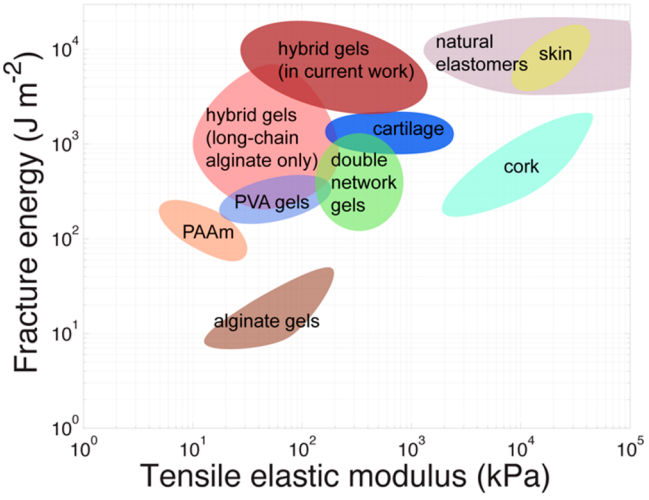

Figure 1. Fracture energies and tensile elastic moduli of various materials. The hybrid gels in the current work are compared with other soft materials, including hybrid gels with long-chain alginate only,[13] double network hydrogels,[22,39] poly(vinyl alcohol) hydrogels (PVA),[40] cartilage,[20,21] natural elastomers,[21,41] skin,[21,42] and cork[21] along with data for polyacrylamide hydrogels (PAAm) and alginate hydrogels.[13]

ionic cross-links in the alginate network over a large region of the hydrogel (Figure 2c).[13]

The viscosity of an aqueous solution of alginate depends on both the concentration and chain length of the alginate.[28−30] Alginate is a natural product available only with specific chain lengths. Modification of the chain length requires special treatments such as γ-ray irradiation, which may also introduce changes in the distribution of the uronate residues.[31] We used two types of biologically derived alginates that differ in the chain length but not in the distribution of the uronate residues: LF20/40, a long-chain alginate with a molecular weight of 200 kg mol^{-1}; and LFR5/60, a short-chain alginate with a molecular weight of 30 kg mol^{-1}.[32,33] Both alginates are commercially available (FMC BioPolymer). In an aqueous solution containing both alginates, the viscosity reduces as the fraction of the short-chain alginate increases (Supporting Information, Figure S1). The solution of the short-chain alginate has a low viscosity even at a high concentration of alginate (Supporting Information, Figure S2).

We increase the ionic cross-link density by using a combination of calcium sulfate and calcium chloride. The cross-linker used in our previous work, $CaSO_4{\cdot}2H_2O$, has low solubility in water (2.4 g L^{-1} at 20 °C);[13] $CaSO_4{\cdot}2H_2O$ cannot supply sufficient dissolved Ca^{2+} ions to achieve a high cross-link density (Supporting Information, Figure S3). The solubility of $CaCl_2$ is high, but the direct use of $CaCl_2$ as a cross-linker causes inhomogeneous distribution of alginate in pure alginate hydrogels.[30,34] Here we show that $CaCl_2$ can be used to synthesize alginate-polyacrylamide hydrogels with homogeneous distribution of alginate. Our new protocol of synthesis is as follows. A homogeneous alginate-polyacrylamide hydrogel was first formed with $CaSO_4{\cdot}2H_2O$; the cross-link density of G blocks was low, but alginate chains were immobilized in the network. Subsequently, the hydrogel was immersed in a large volume of a 1.0 M $CaCl_2$ solution to achieve full cross-linking of G blocks while retaining the homogeneous distribution of alginate in the hydrogel. This observation is consistent with a recent report.[35]

We demonstrate that the concentration of alginate strongly affects the properties of alginate-polyacrylamide hydrogels. In a series of experiments, we fixed the ratio of polyacrylamide to water at 16.8 wt % and fixed the ratio of short-chain to long-chain alginates at 4:1 but varied the concentration of alginate from 2.3% to 6.4%; the swelling ratio, defined as the ratio of the volume of the hydrogel to that of the dry polymer, changed from 7.0 to 6.0 with increasing alginate content. The G blocks on the alginate chains were fully cross-linked (Supporting Information, Figure S4). We then performed a series of tensile tests on both unnotched and notched samples. For the tensile tests of unnotched samples, as the concentration of alginate

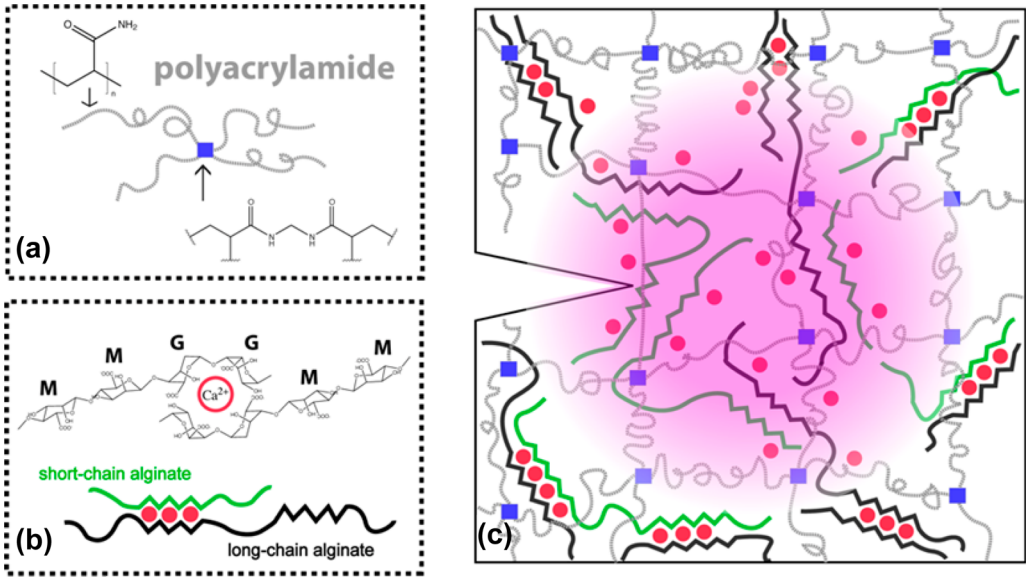

Figure 2. Structure and toughening mechanism of hybrid hydrogels. (a) Polyacrylamide (PAAm; gray dashed lines) forms covalent cross-links through *N*,*N*′-methylenebis(acrylamide) (MBAA; blue squares). (b) Short- and long-chain alginate chains (green and black solid lines, respectively) with G blocks that form ionic cross-links through Ca^{2+} (red circles). (c) Large area of plastic zone (pink region) present ahead of the notch where ionic cross-links unzip to dissipate energy.

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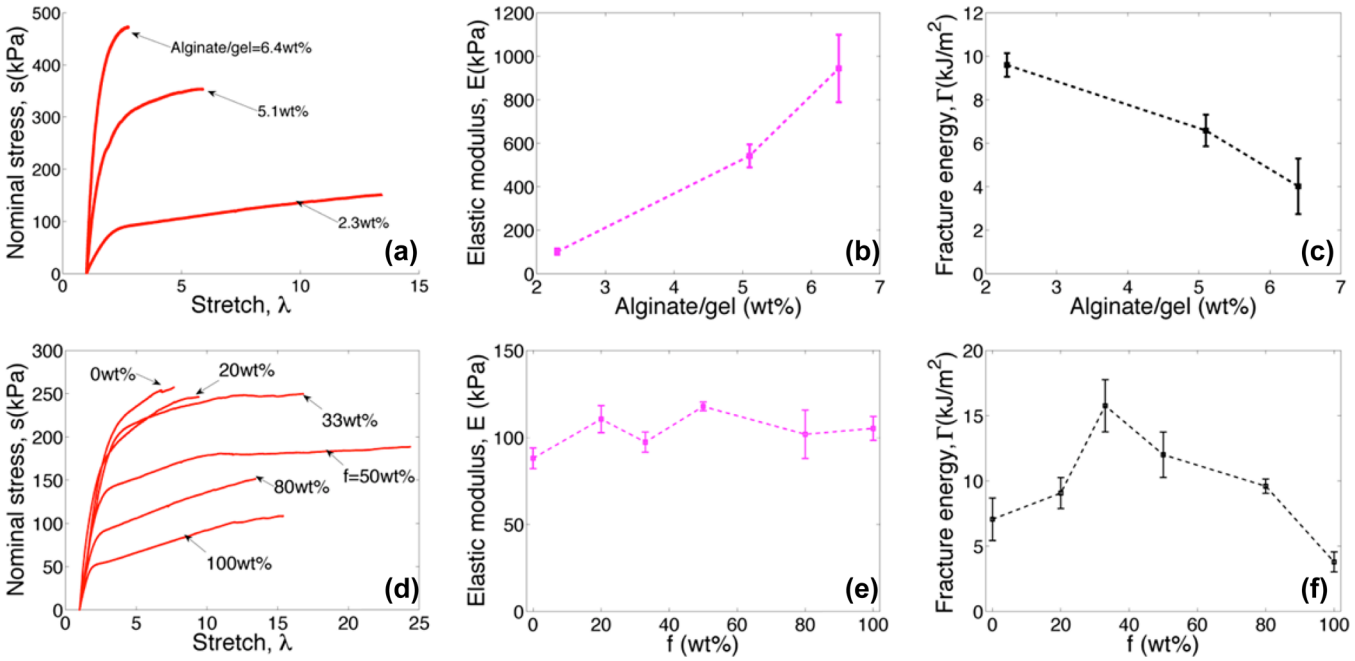

Figure 3. Properties of hybrid hydrogels. (a) Stress−stretch curves of gels of various concentrations of alginate. Each test was performed by pulling an unnotched sample to rupture. (b) Elastic modulus as a function of the concentration of alginate in the gel. (c) Fracture energy varies with the concentration of alginate. (d) Stress−stretch curves of gels of various fractions of short-chain alginate to the total alginate. (e,f) Elastic modulus (e) and fracture energy (f) vary with the fraction of short-chain alginate. Error bars show standard deviation; sample size $n = 4$.

increases, the strength increases, but the rupture stretch decreases (Figure 3a). The nominal stress is the loading force divided by the cross-sectional area of the undeformed sample. The stretch is the current length divided by the initial length of undeformed sample. The elastic modulus is the slope of the initial portion of the stress−stretch curves. As the alginate content increases, the elastic modulus of the hydrogel increases (Figure 3b). The fracture energy of the hydrogel was measured by performing tensile tests on notched samples using a geometry known as the pure shear test.[13,36] The fracture energy of the hydrogel decreases with increasing alginate content (Figure 3c). Despite this reduction, the hydrogel with the maximum alginate content maintains a large fracture energy of 4 kJ m^{-2} while exhibiting a large elastic modulus of 1000 kPa.

We interpret this inverse relation between stiffness and toughness as follows. Increasing the alginate content not only raises the stiffness of the hydrogel but also its strength (Figure 3a). The high strength, in turn, lowers the toughness of the hydrogel because the region near the crack tip where energy is dissipated during crack growth decreases in size with increasing strength. The trade-off between strength and toughness is well recognized in materials science.[37,38]

Our new approach breaks this inverse relation between stiffness and toughness. In pure alginate hydrogels, the chain length affects strength but not stiffness (Supporting Information, Figure S5). The same phenomenon occurs in alginate-polyacrylamide hydrogels. We varied the weight percentage of short-chain alginate in the gels, f, while fixing the total weight percentage of alginate at 2.3 wt % and the ratio of $CaSO_4$ to alginate at 20 wt %. The strength of the hydrogel decreases as the fraction of short-chain alginate increases (Figure 3d), while the elastic modulus is independent of the fraction of short-chain alginate (Figure 3e). The fracture energy reaches a maximum value of 16 kJ m^{-2} at an intermediate proportion of short- and long-chain alginates (Figure 3f). The maximum value of the fracture energy is a 2-fold improvement over the highest value reported before for alginate-polyacrylamide hydrogels with long-chain alginate only.[13] It is perhaps the first time that a hydrogel containing around 90% water rivals natural elastomers in toughness (Figure 1). Furthermore, we can independently optimize the stiffness and toughness of a hydrogel by varying the molecular weight and cross-link density of the alginate (Supporting Information, Figure S6).

We interpret the observed relation between the fracture energy and the fraction of short-chain alginate as follows. In the alginate-polyacrylamide hydrogel containing only long-chain alginate, the strength is so high that only a small region around the root of the notch is stressed enough to unzip ionic cross-links, leading to a low fracture energy (Supporting Information, Figure S7a). As the fraction of short-chain alginate increases, the strength decreases, and the size of the region in which ionic cross-links unzip grows, leading to an increase in fracture energy (Supporting Information, Figure S7b). When the content of the short-chain alginate is too large, the strength of the alginate network is too low to effectively contribute to energy dissipation. Thus, the fracture energy goes through a maximum at an intermediate fraction of short-chain alginate.

In summary, this work demonstrates a significant improvement of stiffness and toughness of alginate-polyacrylamide hydrogels. By using a combination of short- and long-chain alginates, calcium sulfate, and calcium chloride as cross-linkers, we can increase the concentration of alginate and ionic cross-link density and optimize the stiffness and toughness of hydrogels independently. These hybrid hydrogels are accessible to a very large range of stiffness and toughness combinations, extending significantly beyond traditional benchmarks. The combination of high stiffness, high toughness, biocompatibility, and facile synthesis makes these hydrogels ideal candidates for further development as load-bearing materials.

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EXPERIMENTAL SECTION

Hydrogel Synthesis. Alginate-polyacrylamide hydrogels were synthesized using the following protocol. Sodium alginate (LFR5/60 and LF20/40) and acrylamide (AAm) were dissolved in distilled water. The weight of AAm was fixed at 0.168 times that of water. The mixture was stirred for 2 days at room temperature until the solution became homogeneous. The mixture was subsequently mixed with *N,N′*-methylenebis(acrylamide) (MBAA), tetramethyl-ethylenediamine (TEMED), $CaSO_4{\cdot}2H_2O$, and ammonium persulfate (APS) in this sequence. The weights of MBAA, TEMED, and APS were fixed at 0.0006, 0.0055, and 0.006 times that of AAm. The weight of alginate and $CaSO_4$ was varied as noted earlier. The mixture was then placed in a glass mold ($75 \times 45 \times 3$ mm^3) and cured by UV (OAI LS 30 UV flood exposure system, 350 W, wavelength 365 nm) for 200 s. The product was kept at room temperature overnight to ensure complete reaction. A combination of $CaSO_4$ and $CaCl_2$ was used as cross-linkers; the concentration of $CaSO_4{\cdot}2H_2O$ was fixed at 19.4 mM during gelation, and then the samples were submersed in a large volume of 1.0 M $CaCl_2$ solution for at least 3 days.

Mechanical Testing. A rectangular strip of the hybrid hydrogel ($75 \times 45 \times 3$ mm^3) was glued to two rigid acrylate clamps ($75 \times 20 \times 1.5$ mm^3). For notched samples, an edge crack of length 35 mm was cut using a razor blade in the middle of the gauge section of the sample. An Instron machine (model 3342 with load cell of maximum 1000 N) was used for tensile tests. The stretch rate was 2 min^{-1}. The signals of force and extension were recorded by the Instron machine throughout the test.

ASSOCIATED CONTENT

Supporting Information

Viscosity of alginate solutions, low solubility of calcium sulfate, soaking hydrogels, compression tests of alginate hydrogels, effects of ionic cross-link density, and effects of alginate chain length. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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