

# Topological Adhesion of Wet Materials

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**Achieving strong adhesion between wet materials (i.e., tissues and hydrogels) is challenging. Existing adhesives are weak, toxic, incompatible with wet and soft surfaces, or restricted to specific functional groups from the wet materials. The approach reported here uses biocompatible polymer chains to achieve strong adhesion and retain softness, but requires no functional groups from the wet materials. In response to a trigger, the polymer chains form a network, in topological entanglement with the two polymer networks of the wet materials, stitching them together like a suture at the molecular scale. To illustrate topological adhesion, pH is used as a trigger. The stitching polymers are soluble in water in one pH range but form a polymer network in another pH range. Several stitching polymers are selected to create strong adhesion between hydrogels in full range of pH, as well as between hydrogels and various porcine tissues (liver, heart, artery, skin, and stomach). The adhesion energy above  $1000 \text{ J m}^{-2}$  is achieved when the stitching polymer network elicits the hysteresis in the wet materials. The molecular suture can be designed to be permanent, transient, or removable on-demand. The topological adhesion may open many opportunities in complex and diverse environments.**

Existing and emerging medical practices have posed a persistent, fundamental challenge: creating strong adhesion between wet materials—living tissues and synthetic hydrogels—under physiological conditions. Applications include tissue repair,<sup>[1,2]</sup> wound dressing,<sup>[1,3]</sup> and drug delivery.<sup>[4]</sup> Also under intense development are implantable devices for energy harvesting,<sup>[5]</sup> neural stimulation and recording,<sup>[6]</sup> sensing,<sup>[7]</sup> and actuation.<sup>[8]</sup> Existing adhesives are weak, or toxic, or incompatible with wet and soft surfaces, or restricted to specific functional groups from the wet materials. For example, cyanoacrylate is a strong adhesive, but is cytotoxic, and forms a glassy phase and hardens the interface.<sup>[9]</sup> Nanoparticles,<sup>[10]</sup> bridging polymers,<sup>[11]</sup> fibrin,<sup>[12]</sup> and poly(ethylene glycol) gels<sup>[13]</sup> are facile, but the adhesion energy is low ( $1\text{--}10 \text{ J m}^{-2}$ ), due to either weak bonds or fragile materials. A family of recently developed adhesives achieve adhesion energy of  $1000 \text{ J m}^{-2}$ , but the adhesion relies on functional groups from the tissues and hydrogels,<sup>[1]</sup> and cannot bond hydrogels without suitable functional groups.

Here we report an approach that molecularly stitches wet materials. Each wet material, to be called an adherend, has a preexisting polymer network. The molecular stitch uses polymer chains to form a new polymer network, in response to a trigger. This new polymer network is localized at the interface between the two adherends, and in topological entanglement with the network of the adherend on either side. It is through this topological entanglement that the new polymer network stitches the two preexisting polymer networks. To debond, the topologically entangled networks must disentangle—that is, at least one of the three networks must break. We call the polymer chains the stitching polymers, and their network the stitching polymer network. We call this bonding method topological adhesion, or topohesion for brevity, and call the solution of the stitching polymers the topohesive. The stitching polymer network functions as a molecular suture.

Our hypothesis is twofold. First, polymer chains can be triggered to form a network, localized at the interface of two adherends, and in topological entanglement with the preexisting networks of the adherends. Second, the stitching polymer network can be flexible enough to retain the softness of the adherends, and yet strong enough to achieve adhesion energy comparable to the bulk toughness of the adherends by eliciting the hysteresis in the adherends, without requiring any functional groups from the adherends. (Functional groups may exist in tissues and hydrogels for other reasons, but need not form any bonds with the stitching polymers.)

Topological entanglement has played fundamental roles in polymers.<sup>[14]</sup> It has in recent decades led to hydrogels and elastomers of exceptional modulus, strength, and toughness.<sup>[15–18]</sup> Topological entanglement has also been used to achieve adhesion by diffusing monomers into adherends and polymerizing in situ.<sup>[19,20]</sup> Such a bonding method starts with monomers, and often involves invasive and toxic chemical reactions, as well as ultraviolet irradiation. No attempt has been reported to trigger polymer chains to form a stitching network and achieve strong adhesion between hydrogels and tissues.

We illustrate topological adhesion by using pH as a trigger. This pH-triggered topological adhesion mimics the formation of strong byssal threads by a mussel (*Mytilus californianus* Conrad 1837).<sup>[21]</sup> When a foot of the mussel attaches to a surface, the distal depression of the foot secretes an aqueous solution of proteins at  $\text{pH} \approx 3$ . When the foot lifts off, the surrounding seawater of  $\text{pH} \approx 8$  flows in, and the proteins form a strong network.

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To formulate a topohesive, we use polymer chains that dissolve in water in one pH range and form a polymer network in another pH range. We prepare an aqueous solution of the stitching polymer chains at one value of pH. The two adherends have another value of pH, representative of that in a physiological environment. We place the solution of the stitching polymer chains between the two adherends. In response to the pH in the adherends, the polymer chains form a third network. We readily achieve adhesion energy above  $1000 \text{ J m}^{-2}$  when the stitching polymer network elicits hysteresis in the wet materials. By choosing different species of stitching polymers, we achieve strong adhesion in full range of pH. We bond hydrogels to various porcine tissues (liver, heart, artery, skin, and stomach). Furthermore, the molecular suture is removable, on-demand, by changing the pH back to the soluble range of the polymer chains.

To ascertain our hypothesis, we first bond two pieces of hydrogels using chitosan chains. Hydrogels are relatively simple and well-characterized systems, and structurally similar to living tissues and extensively used in medicine.<sup>[7,22]</sup> Chitosan chains are biopolymers widely used in bioengineering.<sup>[23]</sup> The amine groups on chitosan are responsive to changes in pH.<sup>[24]</sup> The dissociation  $[\text{NH}_3^+] \rightleftharpoons [\text{NH}_2] + [\text{H}^+]$  has the equilibrium constant  $K_a = [\text{NH}_2][\text{H}^+]/[\text{NH}_3^+]$ . By definition  $\text{p}K_a = -\log[K_a]$  and  $\text{pH} = -\log[\text{H}^+]$ , so that  $\log[\text{NH}_2] - \log[\text{NH}_3^+] = \text{pH} - \text{p}K_a$ . For chitosan,  $\text{p}K_a = 6.5$ . When  $\text{pH} < 6.5$ ,  $[\text{NH}_2] < [\text{NH}_3^+]$ , and the chitosan chains dissolve in water as a polyelectrolyte (Figure 1a). When  $\text{pH} > 6.5$ ,  $[\text{NH}_2] > [\text{NH}_3^+]$ , and the  $\text{NH}_2\text{--OH}$  hydrogen bond promotes the chitosan chains to form a network (Figure 1b).<sup>[24,25]</sup>

We prepared an aqueous solution of chitosan of pH 5, and placed the solution between two hydrogels of pH 7 (Figure 1c). The chitosan chains diffused into the two hydrogels and, in response to the pH in the hydrogels, formed a third network (Figure 1d). We have hypothesized that the chitosan network is localized at the interface, in topological entanglement with the networks of the two hydrogels. Whether such a chitosan network will form depends on two concurrent kinetic processes: the diffusion of chitosan chains into the hydrogel, and the formation of the chitosan network.

To confirm the formation of the chitosan network localized at the interface, we labeled the chitosan chains with fluorescein isothiocyanate (FITC), and tracked their diffusion using confocal microscopy (Figure 1e). In the first hour, the chitosan chains diffused away from the interface, shown by the gradual thinning of the chitosan-rich layer and the thickening of the diffusion layer. However, fewer chitosan chains diffused away in the next few hours, and finally chitosan chains ceased to diffuse at 24 h. As a comparison, when we placed the same chitosan solution between two hydrogels of pH 5, the chitosan chains kept diffusing into the hydrogels, and no chitosan network formed (Figure S1, Supporting Information).

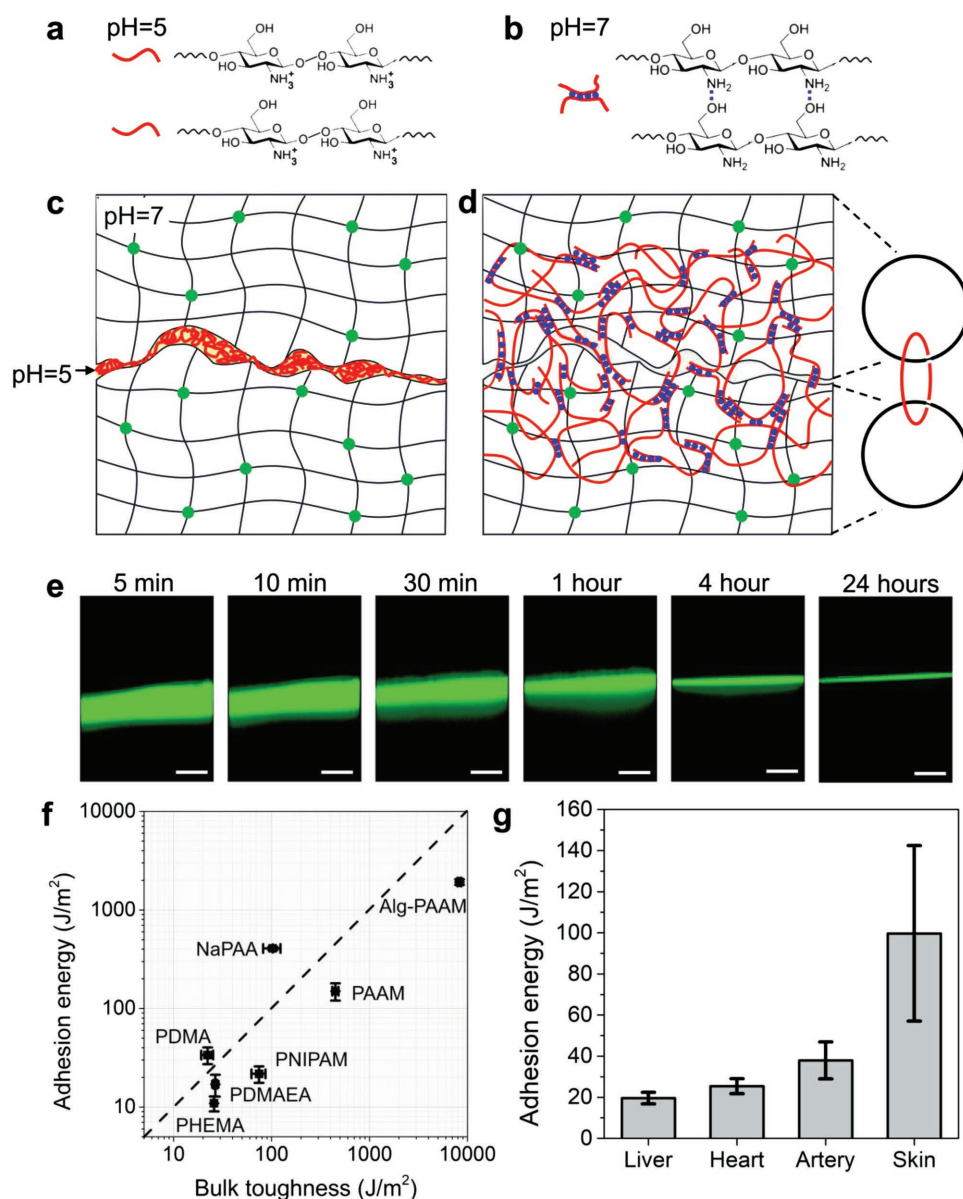
According to the Rouse model,<sup>[26]</sup> the diffusivity of a chitosan chain in water is  $D = kT/(N\eta b)$ , where  $kT$  is the temperature in the unit of energy,  $\eta$  is the viscosity of water,  $b$  is the size of the repeating unit of the chitosan chain, and  $N$  is the number of the repeating units. Taking  $kT = 10^{-21} \text{ J}$ ,  $\eta = 10^{-3} \text{ Pa s}$ ,  $b = 10^{-9} \text{ m}$ , and  $N = 1000$ , we obtain that  $D \approx 10^{-12} \text{ m}^2 \text{ s}^{-1}$ , which is much lower than the diffusivity of  $\text{H}^+$  and  $\text{OH}^-$  ( $\approx 10^{-9} \text{ m}^2 \text{ s}^{-1}$ ). The

time scale is estimated as  $h^2/D \sim \text{hours}$ , where  $h$  is the diffused chitosan thickness ( $\approx 100 \mu\text{m}$  from the confocal image). This estimate roughly agrees with our experimental observation.

We further ascertain the formation of chitosan network in topological entanglement with the networks of the hydrogels by measuring the adhesion energy. The dissociation energy of a hydrogen bond is weak ( $\approx 10kT$ ) compared to that of a covalent bond ( $\approx 140kT$ ).<sup>[27,28]</sup> However, tens to hundreds of hydrogen bonds in aggregation result in a high bonding energy.<sup>[29]</sup> The network of pure chitosan is still fragile, but the chitosan network in topological entanglement with the network of the adherends achieves adhesion energy comparable to the bulk toughness of the adherends (Figure 1f, Table S1, Supporting Information). For example, the bulk toughness of poly(dimethylacrylamide) (PDMA) is  $\approx 22 \text{ J m}^{-2}$ , and the adhesion energy is  $\approx 33 \text{ J m}^{-2}$  the bulk toughness of alginate–polyacrylamide (Alg-PAAM) is  $\approx 8000 \text{ J m}^{-2}$ , and the adhesion energy is  $\approx 2000 \text{ J m}^{-2}$ . Moreover, the bonded hydrogels are stretchable and transparent (Figure S3, Supporting Information).<sup>[30]</sup> We also used chitosan chains to stitch polyacrylamide (PAAM) hydrogel to various porcine tissues: liver, heart, artery, and skin (Figure 1g). The skin exhibits a relatively high toughness among the soft organs ( $\approx 1000 \text{ J m}^{-2}$ ),<sup>[31]</sup> thus the corresponding adhesion energy is also high ( $\approx 100 \text{ J m}^{-2}$ ).

The procedure for preparing adhesion can greatly affect the adhesion energy. To illustrate some of the effects, we spread a chitosan solution on one piece of PAAM hydrogel, placed another piece of PAAM hydrogel on top, and compressed the two hydrogels with a strain  $d/L$  (Figure 2a). The maximum adhesion was achieved at the combination of a solution of  $500 \mu\text{m}$  thickness and a strain of 5.5%, and the thinner chitosan layer and larger strain lead to weaker adhesion energy (Figure 2b). We monitored the change of adhesion energy over time, and found that the adhesion energy established to  $\approx 50 \text{ J m}^{-2}$  within 30 min, and then approached an equilibrium value of  $\approx 150 \text{ J m}^{-2}$  after 24 h (Figure 2c). The slow kinetics may be associated with the slow formation of the chitosan network. Similar phenomena have been observed in the aging of polyacrylamide–poly(vinyl alcohol) (PAAM–PVA) hydrogels<sup>[32]</sup> and PAAM–chitosan hydrogels,<sup>[30]</sup> as well as in the slow recovery of Alg–PAAM hydrogels.<sup>[16]</sup> For topological adhesion, the kinetics of adhesion depend on stitching polymers. For example, poly(4-aminostyrene) (PAS) reached adhesion energy of  $\approx 300 \text{ J m}^{-2}$  within the first 15 min, and saturated to  $\approx 400 \text{ J m}^{-2}$  after 10 h (Figure S4, Supporting Information). The controlled kinetics of adhesion may find clinical advantages, as the initial relatively small adhesion is often sufficient to hold tissues or hydrogels,<sup>[1,10]</sup> but allows repositioning. In addition, the chitosan chains need to be sufficiently concentrated and long to ensure strong adhesion (Figure 2d,e).

The fluids in human tissues vary greatly in pH.<sup>[33]</sup> The blood, the cerebrospinal fluid, and the cellular fluid of muscle and skin are nearly neutral (pH 6–7.4), the pancreatic fluid and bile are alkaline (pH 7.6–8.8), and the gastric fluids are extremely acidic (pH 1–3.5). We next used several species of stitching polymers to achieve strong adhesion in full range of pH. In addition to chitosan, which forms a network when  $\text{pH} > 6.5$ , we used three other species of stitching polymer chains: PAS forms a network when  $\text{pH} > 4.6$ , alginate (Alg) forms a network when  $\text{pH} < 3.5$ , and cellulose forms a network when  $\text{pH} < 13$  (Figure 3a, Table S2, Supporting Information). We used the



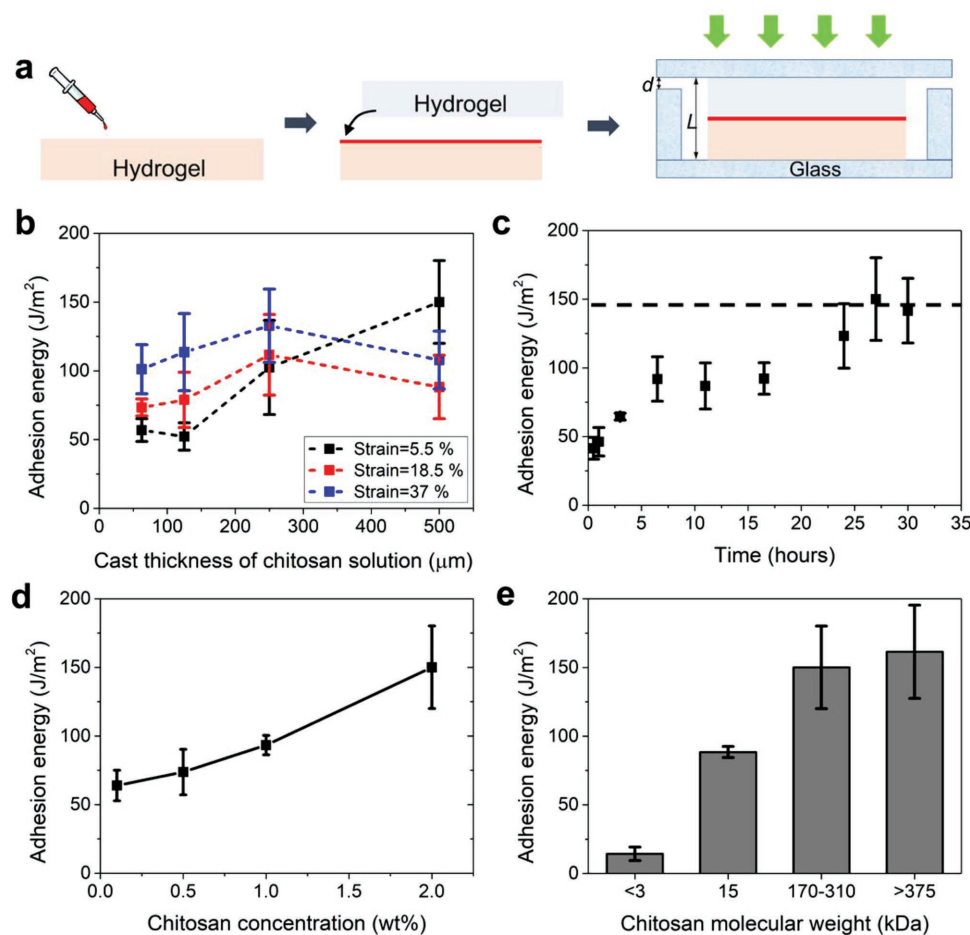
**Figure 1.** Topological adhesion. a) Chitosan chains dissolve in water at pH 5. b) Chitosan chains form a network in water at pH 7. c) Place an aqueous solution of chitosan of pH 5 between two hydrogels of pH = 7. d) The chitosan chains diffuse into the two hydrogels and form a network, which topologically entangles with the networks of the two hydrogels. e) A chitosan solution is placed between two pieces of polyacrylamide hydrogels. A sequence of confocal microscopic images show that the chitosan chains diffuse away from the interface in the first hour, diffuse less for the next few hours, and cease to diffuse at 24 h. The scale bar is 300  $\mu\text{m}$ . f) The adhesion energy of the chitosan-stitched hydrogel is plotted against the bulk toughness of the hydrogel. The hydrogels used are listed in Table S1 (Supporting Information). g) The adhesion energy of chitosan-stitched PAAM hydrogel and various tissues. The data represent the mean and standard deviation of four to six experimental results.

four species of polymers to bond PAAM hydrogels of various values of pH, and confirmed that adhesion was established only when the pH of the hydrogels was in the network-forming range of each species of the stitching polymers (Figure 3b–e).

In the network-forming range of pH, the adhesion energy is low when the pH of hydrogel is either close to, or far from, the  $pK_a$  of the stitching polymers, and exhibits a maximum in the middle. We interpret this finding using chitosan as an example. When the pH of hydrogel is close to  $pK_a$  of chitosan, the positively charged amine  $\text{NH}_3^+$  and neutral amine  $\text{NH}_2$  are

comparable in numbers. This may lead to insufficient number of hydrogen bonds and thus a weak chitosan network. When the pH of hydrogel far exceeds  $pK_a$ , the chitosan chains at interface are neutralized to form network much faster, which impedes the diffusion of chitosan chains into both hydrogels. This may lead to insufficient topological entanglements with both hydrogel networks.

Topological adhesion enables the design of adhesives for extreme pH environment. We demonstrated the strong adhesion between a hydrogel and a porcine stomach tissue in an



**Figure 2.** Adhesion energy as a function of several variables. a) Schematics of the bonding procedure. Spread an aqueous solution of chitosan on the surface of one PAAM hydrogel, place the other PAAM hydrogel on top, and compress the two pieces of hydrogels with strain  $d/L$ . b) Adhesion energy varies with the thickness of the chitosan solution and the compressive strain. c) Adhesion energy evolves with time. d) Adhesion energy increases with the concentration of chitosan solution. e) Adhesion energy increases with the molecular weight of chitosan chains. All the data represent the mean and standard deviation of four to six experimental results.

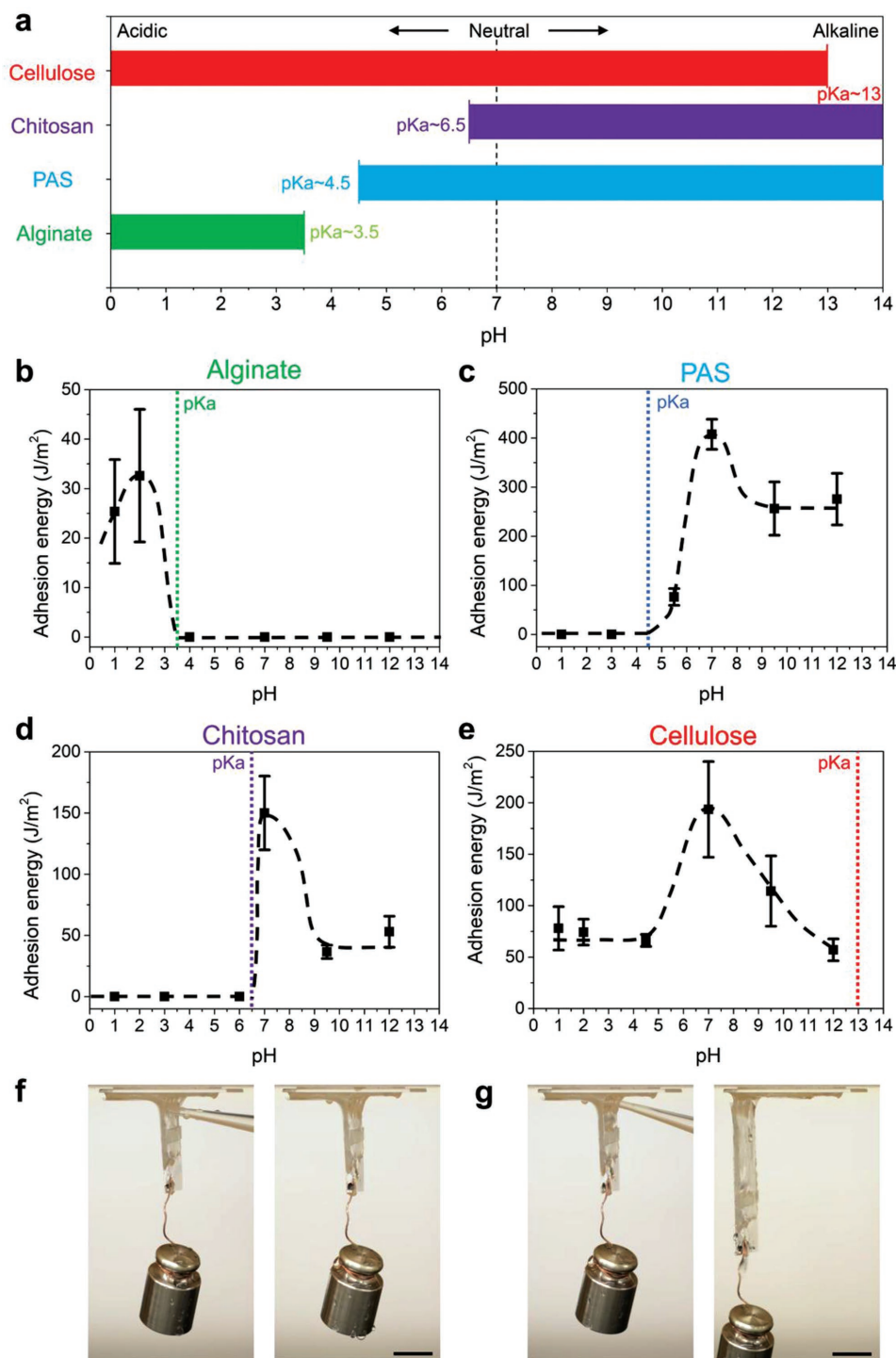
extremely low pH ( $\approx 1.5$ ) with cellulose solution (Figure S5, Supporting Information). The low pH resembles the physiological environment inside the stomach. We tested the bonding by lap shear test. The hydrogel used is much softer than the stomach tissue. The lap-shear test showed that the hydrogel remained firmly bonded to the tissue over a stretch of 11 times of its initial length (Movie S1, Supporting Information).

The molecular stitch is removable, on-demand, when the pH is changed back to the soluble range of the stitching polymers. We demonstrated this capability using chitosan-stitched PAAM hydrogels. We fixed the top hydrogel to a rigid acrylic plate and hung the bottom hydrogel with a weight. The weight itself did not cause debonding. We then dripped water at the bonding front for several times. No debonding was observed after 12 trails of dripping (Figure 3f and Movie S2, Supporting Information). In comparison, we dripped hydrochloric acid (1 M) at the same bonding front. The debonding progressively advanced at every single dripping, until two hydrogels completely detached (Figure 3g and Movie S3, Supporting Information). The capability of on-demand removal of the molecular stitch may motivate future design of smart adhesives or bandages.

Topological adhesion involves three polymer networks: the pre-existing networks of the two adherends, and the newly formed network of the stitching polymers. To disentangle, at least one of the three networks must break. The intrinsic energy to break a network is  $10\text{--}100 \text{ J m}^{-2}$ .<sup>[34–37]</sup> This picture is fundamentally different from polymer chains physically entangled with the networks of two adherends without forming a network. The polymer chains can be disentangled and pulled out without breaking any network, requiring an energy of  $\approx 1 \text{ J m}^{-2}$ .<sup>[38,39]</sup>

To confirm the formation of a strong and stable stitching polymer network, we measured the speed of crack as a function of energy release rate. When a crack extends at a certain speed, the measured energy release rate results from two processes: the disentanglement at the crack front, and the hysteresis in the adherends. The latter effect reduces when the crack speed is low. We measured the energy release rate at crack speeds across many orders of magnitude (Figure 4). For chitosan-stitched PAAM hydrogels, the energy release rate arrives at a constant value of  $\approx 60 \text{ J m}^{-2}$  as the crack speed approaches zero. This relatively high value supports the

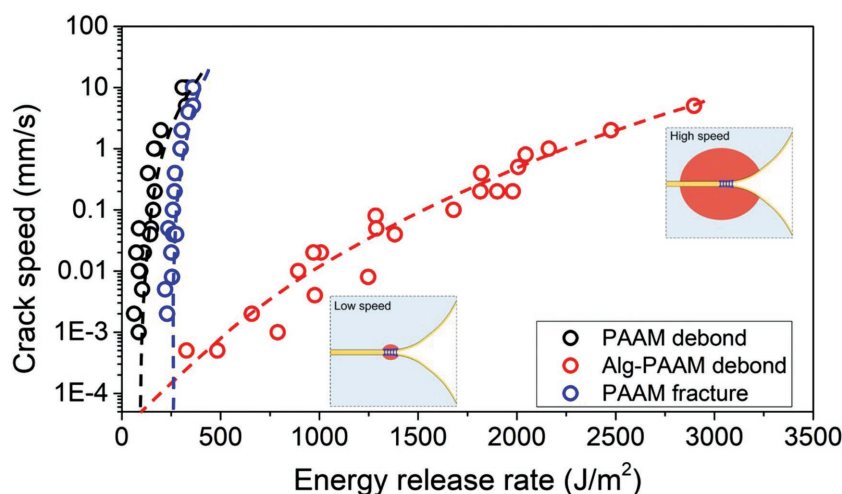




**Figure 3.** Adhesion in full range of pH. a) The ranges in which four species of polymers form networks cover all pH levels. The adhesion energy depends on pH when two pieces of PAAM hydrogels are bonded with each species of polymers: b) alginate, c) PAS, d) chitosan, and e) cellulose. All the data represent the mean and standard deviation of four to six experimental results. Two pieces of PAAM hydrogels were bonded with chitosan. The top hydrogel was attached to a rigid acrylic plate, and the bottom hydrogel was attached to a weight. f) When water was dripped at the bonding front, the hydrogels remained bonded. g) When an acid was dripped at the bonding front, the hydrogels debonded. The scale bar is 2 cm.

hypothesis that the chitosan network and the PAAM network are topologically entangled: the debond breaks at least one of the networks.

To find whether the chitosan network or the PAAM network breaks, we also conducted the slow-crack test for a homogeneous PAAM hydrogel. The energy release rate of



**Figure 4.** Crack speed as a function of energy release rate. Compare three systems: debond of chitosan-stitched PAAM hydrogels, debond of chitosan-stitched Alg-PAAM hydrogels, and fracture of a homogeneous PAAM hydrogel. At any crack speed, the energy release rate of the homogeneous PAAM hydrogel is larger than that of the chitosan-stitched PAAM hydrogels. As the crack speed approaches zero, the energy release rate approaches  $60 \text{ J m}^{-2}$  for debond, and  $250 \text{ J m}^{-2}$  for fracture. For the chitosan-stitched Alg-PAAM hydrogels, the energy release rate increases greatly with the crack speed, but approaches  $60 \text{ J m}^{-2}$  at low crack speed. The insets indicate that the energy release rate results from the synergy of two processes: the breaking of the stitching polymer network and the hysteresis in the hydrogels. The hysteresis in the hydrogels greatly amplifies the energy release rate at high crack speed, but contributes negligibly to the energy release rate at low crack speed. Each data point represents a single test.

the homogeneous PAAM hydrogel is higher than that of the chitosan-stitched PAAM hydrogels at all crack speeds, and arrives at a constant value of  $\approx 250 \text{ J m}^{-2}$  as the crack speed approaches zero. This comparison indicates that the chitosan-stitched PAAM hydrogels disentangled by the breaking of the chitosan network, not the PAAM network. The slow-crack experiment by itself, however, is unable to differentiate whether the chitosan network broke by the scission of the chitosan chains, or by the unzipping of the hydrogen bonds between the chitosan chains.

Topological adhesion confirms a fundamental principle in fracture mechanics: adhesion is strong if debond elicits hysteresis in the adherends. We conducted the slow-crack experiment for chitosan-stitched hybrid Alg-PAAM hydrogels. The stress-stretch curve of an Alg-PAAM hydrogel exhibits pronounced hysteresis.<sup>[35,36,40]</sup> Our slow-crack data shows that the chitosan suture is strong enough to elicit the hysteresis in the Alg-PAAM to achieve strong adhesion. However, the stress-strain curve of the Alg-PAAM hydrogel is rate dependent.<sup>[41,42]</sup> The energy release rate is  $\approx 3000 \text{ J m}^{-2}$  at a crack speed of  $10 \text{ mm s}^{-1}$ , but reduces to  $\approx 400 \text{ J m}^{-2}$  at  $1 \mu\text{m s}^{-1}$ . By extrapolation, the energy release rate approaches  $60 \text{ J m}^{-2}$  as the crack speed approaches zero. The hysteresis in the bulk greatly amplifies the energy release rate at high crack speed, but contributes negligibly to the energy release rate at low crack speed.

In summary, these experiments taken together support the hypothesis that suitable polymers form a network in topological entanglement with the networks of two wet materials, and the topologically entangled networks lead to strong adhesion without requiring any functional groups from the wet

materials. A given species of stitching polymers works for any wet materials upon triggering by an environmental stimulus, so long as the wet materials do not prevent the formation of the stitching polymer network. The topological adhesion can be applied to a large area, so long as the stitching polymers cover the entire bonding area. The stitching polymer network functions as a suture in the molecular scale, and this molecular suture can be designed to be permanent, transient, or removable on-demand. Topological adhesion is general, which is not limited to be triggered by pH but can be potentially triggered by other stimuli such as salt, temperature and light, along with their corresponding responsive polymers. For example, poly(isopropylacrylamide) (PNIPAM) can be used as the thermoresponsive polymer, which forms a network when the temperature is above the lower critical solution temperature. As another example, when gold nanoparticles are mixed into the wet materials, they generate heat upon exposure to light,<sup>[43]</sup> which trigger the topological adhesion using thermoresponsive polymers. It is hoped that the topological adhesion opens a field of devel-

opment to achieve strong adhesion between wet materials, while retaining softness.

## Experimental Section

Details on the materials and methods are available in the Supporting Information.

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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## Conflict of Interest

The authors declare no conflict of interest.

## Keywords

hydrogels, molecular sutures, stitching polymers, tissues, topological adhesion

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