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Ionic control of crack propagation in biopolymer hydrogels

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Abstract

Alginate hydrogels stabilized by ionic interactions, fracture via crosslink unzipping and chain pull-out. It is found that, allowing non-binding ions to diffuse from a drop of brine into the crack tip region, leads to a strong acceleration of the crack. This is ascribed to the exchange between binding (Ca^{2+}) cations and non-binding ones, which facilitates the opening of unit chelating cages. The resulting lowering of the effective energy barrier is found merely entropic. The ion-exchange can be modelled as a rate-limited kinetic process, the order of which is fixed by the electroneutrality requirement, as checked by comparing the effect of monovalent and divalent cations. Although the embrittlement induced by a ionic shock could hinder the use of alginate gels in physiological environments where structural integrity and load-bearing capacity are required, it however can be thought as a powerful analytic tool for studying the nature and spatial extent of the dissipative mechanism at work when fracturing ultra-tough double network (including a ionic one) gels .

Keywords: fracture mechanics ; hydrogels ; alginate ; ion exchange.

1. Cooperative effect of mechanical and chemical stresses on physical gel fracture.

In many modern applications, polymer hydrogels are envisionned as *structural materials*. For instance, tissue engineering aims at using hydrogels as smart, soft and biocompatible *scaffolds* in the process of regenerating organs *in vivo*. Less futuristic applications, such as drug-delivering, wound healing dressings[1], combine the high water content of the hydrogels with their *mechanical resistance* and *structural integrity*. Figure 1 shows a wound dressing made of a polymer gel sheet. When applied to a wound, the gel sheet is submitted to both mechanical and biochemical solicitations. Since premature rupture remains a crucial issue in such applications, care must be taken to prevent accidental punctures or notches from growing and ultimately tearing the dressing apart. The presence of physiologial fluids exudating from the wound makes this task challenging since a nominally subcritical flaw can become unstable and nucleate a crack due to its physiologically modified environment.

Physiological fluids are aggressive towards gels because of both their enzymatic and ionic content. Alginates[2] are polysaccharides extracted from seaweeds, thereby insensitive to human enzymes (e.g. proteases). In the presence of binding ions (e.g. Ca^{2+}) they form ionic gels which slowly degrade in saline solutions due to binding/non binding ion exchange. This process has been identified for long as a potential drawback for biological applications[3] although it is

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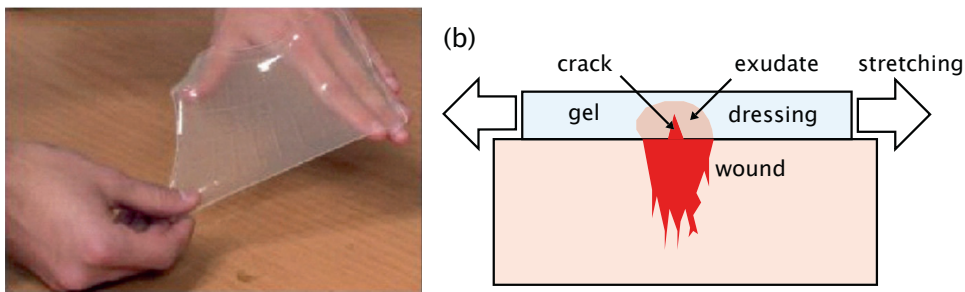 *E-mail address:* tristan.baumberger@insp.jussieu.fr

Fig. 1. (a) An example of a polymeric hydrogel sheet wound dressing. Reprinted with permission from Wound Healing Dressings and Drug Delivery Systems: A Review/JJoshua S. Boateng *et al.*/Journal of Pharmaceutical Sciences Vol. 97. Copyright (c) [2007] Wiley-Liss, Inc. and the American Pharmacists Association. ; (b) Schematic representation of an accidental notch in a dressing, submitted to both mechanical and physico-chemical stresses.

usually very slow (days) *in the absence of mechanical stress* and ultimately ensures the required gel biodegradability[1]. Recently, it has been demonstrated[4] that the double-network association of a covalent network and a ionic alginate one led to a highly stretchable, notch-insensitive hydrogel, *in the absence of non-biding ions*.

In the perspective of load-bearing, physiological applications, it was therefore important to assess the resistance of alginate gels to the *combined* action of stress and ions. This was performed[5] on a model configuration designed to allow the slow, steady propagation of a crack in a calcium-alginate (single network) gel slab, approximately loaded in pure shear. The crack was submitted to a ionic shock by introducing a drop of brine in the tip, allowing non-binding Na^+ ions to diffuse into the gel. Amazingly, the effect on the crack speed was both strong and quasi-instantaneous (see Figure 2), in contradistinction with the above mentionned sluggishness of the ion exchange degradation process.
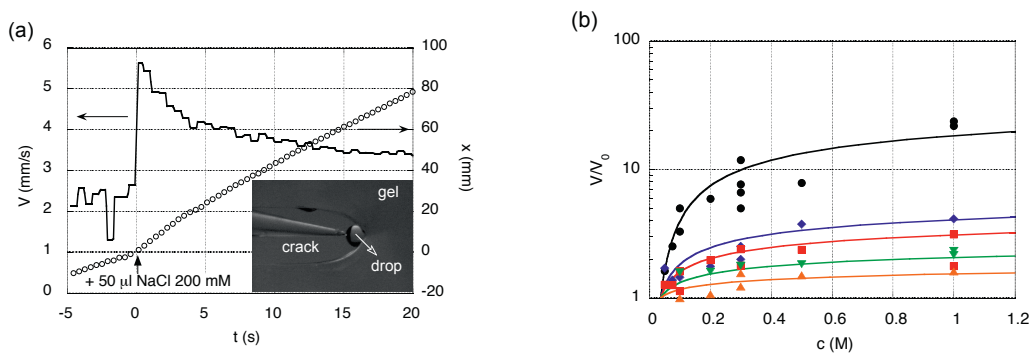

Fig. 2. (a) Velocity of a crack in an alginate gel before and after setting a drop of NaCl solution at physiological concentration right at the crack tip. The crack velocity increases more than two fold with a response time shorter than 100 ms. The crack slowing down towards its initial velocity V_0 results from the progressive empoverishment of the drop in non-binding ions due to their diffusion into the bulk of the slab ; Inset : picture of a crack tip into which a drop of brine is being introduced with a pipette (the diameter of the drop is about 2 mm, setting the scale) ; (b) Relative speeding-up of steady cracks in response to environmental shocks provided by drops of saline concentrations c. Crack openings $\Delta h = 3$ mm ($\bullet$), 4 mm ($\diamond$), 5 mm ($\blacksquare$), 6 mm ($\blacktriangledown$) and 7 mm($\blacktriangle$) control energy release rates in the 1–7 J.m^{-2} range. The whole data set is fitted with a single free parameter according to the model equation described in the text. Reprinted with permission from Cooperative effect of stress and ion displacement on the dynamics of cross-link unzipping and rupture of alginate gels by T. Baumberger and O. Ronsin, *Biomacromolecules* vol. **11**. Copyright 2010 American Chemical Society.

In the following we put emphasis on the enhanced sensitivity to external perturbations of the crack process zone in *physical* gels and describe how this can be taken into account by a minimal model. Finally we discuss the origin of the effect of Na^+, K^+ and Mg^{2+} ions on calcium–alginate gels.

2. Enhanced reactivity of the crack process zone in physical gels.

Physical hydrogels consist of polymer networks that involve cross-link energies intermediate between thermal ($k_B T = 1/40$ eV @300 K) and covalent ones (typ. above 1 eV). As a result, fracture does not proceed via chain scission but rather via the unzipping of the cross-link zones, the latter playing the role of mechnical fuses[6]. *Biopolmyer* gels feature smart examples of such physical crosslinks, for instance H-bond stabilized triple helices in gelatin or egg-boxes in alginate. The latter consist of the association of two suitably conformed moties, made of chelating cages (*boxes*) stabilized by ions (*eggs*), e.g. Ca^{2+}. Mechanical tension on the chains, intensified in the crack-tip vicinity, ultimately opens the cages and unzips the crosslink. Finally, rupture is completed by pulling the uncross-linked chains out of the gel matrix, perpendicular to the crack plane, at the cost of chain/solvent viscous friction. The latter is responsible for the marked rate-dependence of the fracture energy $\mathcal{G}(V)$ which ensures a steady crack propagation solution at a subsonic velocity V for any energy release rate above a Grifith threshold $\mathcal{G}_0$.

Since the energy barrier to be overcome is typically $10\, k_B T$, unzipping is sensitive to thermal activation[8]. Actually, even minute perturbations of the cross-link environment that are able to lower the binding energy barrier will promote premature unziping events, thereby readily resulting in a speeding-up of the crack. The "process zone" of a steady propagating tip in a physical gel therefore consists of chains stretched taut and crosslinks on the verge of disassembling (see Fig.3). It is therefore a strongly "reactive" zone. Moreover, due to the large solvent content (typ. 99% in alginate gels), this zone can readily exchange solute with the tip environment. More precisely, if a solute diffuses with a diffusion coefficient D, it will pervade a zone of depth $L_{\mathrm{diff}} \sim D/V$ with V the crack velocity. Dealing with ions for which $D \sim 10^{-9}$ m^2.s^{-1}, for typical velocities $V < 10^{-2}$ m.s^{-1} the diffusive skin depth is $L_{\mathrm{diff}} > 100$ nm, that is, larger than the process zone size, as determined experimentally[6] for a physical (gelatin) gel. We will therefore consider the process zones of the slow cracks studied here as in chemical equilibrium with the drop.
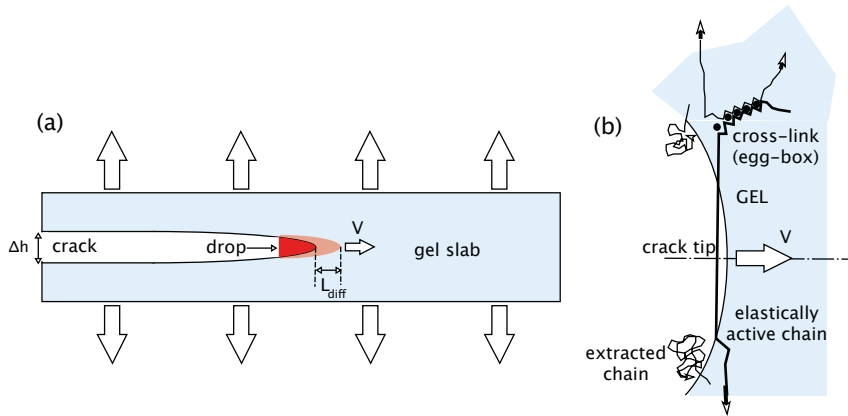

Fig. 3. (a) Schematic representation of a crack in pure shear loading. The energy release rate is fixe by the remote crack-tip opening Δh. When the crack propagates at a constant velocity V, solute (e.g. ions) diffuses from the drop to the gel over a skin length L_{diff} ; (b) Schematic representation of the process zone showing a polymer chain (thick line) being gradually pulled out of the gel while an "egg-box" cross-link is being unzipped. When the cross-link is on the verge of being disassembled, the slightest thermal of chemical kick will increase the unzipping rate, hence the crack velocity.

In order to understand the role of ions in the fracture process of alginate gels, we recall here the minimal ingredients required to account for the $\mathcal{G}(V)$ characteristics as measured in (gelatin or alginate) physical gels[8]. Our approach is based on the cohesive zone model[9] which connects the fracture energy $\mathcal{G}$ to the characteristics of what we have reffered to as the process zone, where chains are being gradually pulled out of the matrix while cross-links unzip (see Fig.3).

$$\mathcal{G} = \bar{\sigma}_{\mathrm{tip}} \Lambda \tag{1}$$

with $\bar{\sigma}_{\mathrm{tip}}$ the average opening stress over the cohesive zone and Λ the maximum crack tip opening of this zone.

On the one hand, it is clear that as no chain scission is allowed, Λ is the length of the polymer chain when stretched taut, therefore a mere material characteristics. On the other hand, $\bar{\sigma}_{\text{tip}}$ depends both on the way cross-links unzip and on the chain/solvent friction, and is thereby coupled to the crack velocity V.

In order to compute the $\bar{\sigma}_{\text{tip}}(V)$ relationship, we need a micromechanical model for the unzipping of an egg-box. We assume that ionic bonds break sequentially, each event resulting from the thermally activated jump over an energy barrier U. In presence of a mechanical tension f acting on the the strands emerging from the crosslink, the effective barrier reads :

$$U = U_0 - \Delta U - fa \tag{2}$$

where the "activation length" a must be on the order of the size of a box element[2] (≈ 0.9 nm). Anticipating on the role of ions, we have accounted for a lowering ΔU of the energy barrier. The opening rate therefore read:

$$\nu = \nu_a \exp\left[-\frac{U}{k_B T}\right] \tag{3}$$

with ν_a an attempt frequency.

Finally, the crack avancement is related to the box opening:

$$V = \alpha \nu a \tag{4}$$

with α a mostly geometrical constant[6].

The closure of our model is provided by the relationship between $\bar{\sigma}_{\text{tip}}$ and f which must account for the tension drop along the chain due to the viscous friction against the solvent of viscosity η:

$$\bar{\sigma}_{\text{tip}} = \frac{f + \beta \eta V \Lambda}{\xi^2} \tag{5}$$

with ξ the mesh size of the gel and β another geometrical constant. Note that we have assumed that the stress was born by the polymer network only, in other words that the poroelastic process zone is in a *drained* state[10]. The solvent draining process being diffusive, with a collective diffusion constant[7] $D_{\text{coll}} \approx 10^{-11}$–$10^{-10}$ mm^2.s^{-1}, the depth of the drained zone $V/D_{\text{coll}} > L_{\text{diff}}$ would therefore remain larger than the size of the process zone.

The outcome of equations 1–5 is an analytical expression for the rate-dependent fracture energy[8]:

$$\mathcal{G} = \mathcal{G}_0 \left[1 + \frac{k_B T}{U_0} \ln\left(\frac{V}{V^\star}\right) + \gamma \eta V \right] - \Delta\mathcal{G} \tag{6}$$

where we have lumped the various geometrical constants into parameters γ and $V^\star$. The shift $\Delta\mathcal{G}$ stems readily from the still unknown ΔU.

Figure 4 shows that this expression, though derived using rough approximations, accounts for the experiments on both dry and wetted cracks. The wet characteristics appears merely shifted by a constant amount $\Delta\mathcal{G}$; this gives confidence in ascribing the salt effect to an ion-dependent lowering of the energy barrier ΔU.

3. Binding vs. non-binding ion exchange: Strength in numbers.

Once $\mathcal{G}_0$, U_0, γ and $V^\star$ are determined by fitting the dry crack data, one can make use of the extensive data set of Fig. 2.b to infer the expression of $\Delta U(c)$ with $c = [\text{Na}^+]$ in the drop. This leads to the following empirical expression[5]:

$$\Delta U \simeq 2 k_B T \ln(c/c_0) \tag{7}$$

The meaning of c_0 is the following: since the alginate we used was a sodium salt, there were already some Na$^+$ ions in the process zone of dry cracks whence $c_0 = 40$ mM is the concentration of a drop of brine which would be in ionic equilibrium with the gel as prepared. Indeed we found that c_0 was fully compatible with the amount of sodium free counterions in the gel, once accounted for the Manning condensation of some Na$^+$ due to the high charge density of alginate. Finally, we were able to fit all the data of Fig. 2.b with the same value of c_0 and no other fitting parameter. This gives strong confidence in our simple model and urges us to get some insight into the physical meaning of eq.7.
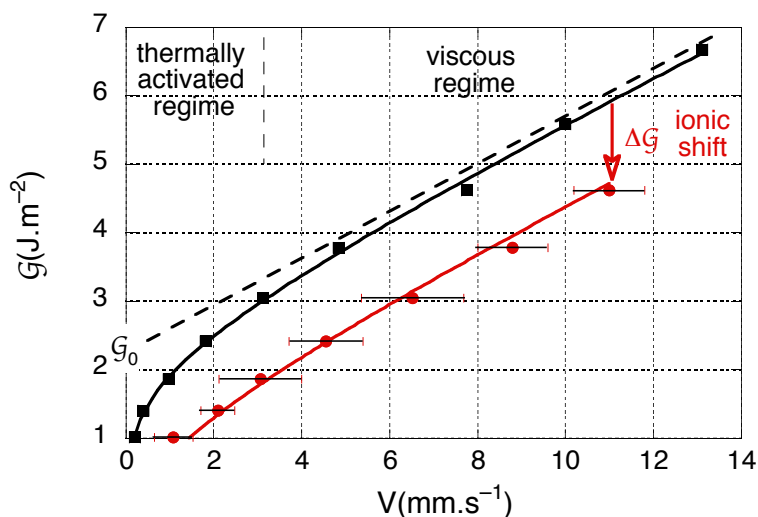
Fig. 4. $\mathcal{G}(V)$ characteristics for cracks without (black squares and line) and with (red circles and line) a drop of 200 mM NaCl in the tip. Lines are fit according to eq.6. Reprinted with permission from *Cooperative effect of stress and ion displacement on the dynamics of cross-link unzipping and rupture of alginate gels* by T. Baumberger and O. Ronsin, Biomacromolecules vol. 11. Copyright 2010 American Chemical Society.

Inserting the expression for $\Delta U(c)$ into eq.3 yields:

$$\nu = A \exp\left[-\frac{U_0 - fa}{k_B T}\right] \times c^2 \tag{8}$$

with A a constant. This expression is strongly reminiscent of the kinetic equation for a second order chemical reaction, i.e. implying two Na^+ for a single opening event. This can be interpreted as follows: the opening of a box element (chelating cage) requires to remove a Ca^{2+} which must be replaced by two Na^+ in order to preserve electroneutrality. Note that this does not mean that these ions will subsequently remain fixed in space (they are *non*-binding) but that they must exchange with the divalent calcium in the activated state corresponding to the energy barrier U. In the vicinity of that state, the calcium ion is on the verge of escaping from the ajar cage. Sodium ions constantly attempt to push the calcium one out of the box; the more numerous the are, the more likely it is they succeed. This description amounts to say that the $Ca^{2+} \leftrightarrow Na^+$ exchange is purely an *entropic* effect. The greater efficiency of the process, as compared to the slow degradation of the alginate gel left at rest in a saline solution, results from the argument of the exponential Arrhenius term being reduced to almost zero by the mechanical bias.

4. Are divalent Mg^{2+} binding ions ?

The role of ions in the kinetics of cross-link unzipping in alginate gels may look surprizingly simple. The above scenario is therefore worth being checked against changing the nature, and more importantly the valence of the non-binding exchange ions. We have reproduced the experiments and analysis of Baumberger & Ronsin[5] using this time brines of KCl and MgCl$_2$. The divalent cation Mg^{2+} is generally reported as *non-binding* for alginate molecules although it has been claimed that with concentrations of alginate and MgCl much larger that those used here, "gels" ultimately form after hours. Our "salted crack" experiment is ideally suited to reveal any binding trend of a cation.

We have therefore determined the shift of the energy barrier, $\Delta U(c)$, for a cation concentration c in the brine, the reference being that of a bare sodium alginate gel with $[Na^+] = c_0$. The results are gathered on Fig. 6. For c ranging between 50 mM and 1 M, ΔU grows quasi-logarithmically, whatever the counterion. While the logarithmic slopes $m = d\Delta U/d \ln c$ of the K^+ and Na^+ data are equal within experimental uncertainty and compatible with $m = 2$, that of the Mg^{2+} data is noticeably smaller and compatible with $m = 1$. This is in full agreement with our simple model
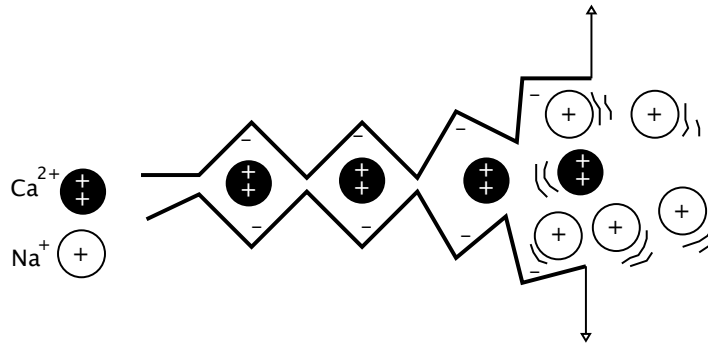
Fig. 5. Schematic representation of an egg-box crosslink zone during unzipping. The numerous Na^+ counterions contribute to pushing the Ca^{2+} ion out of its chelating cage, thereby preserving local electroneutrality.

where m is the order of the ion-exchange "reaction", itself fixed by the valence of the non-binding ion with respect to that of the binding one.
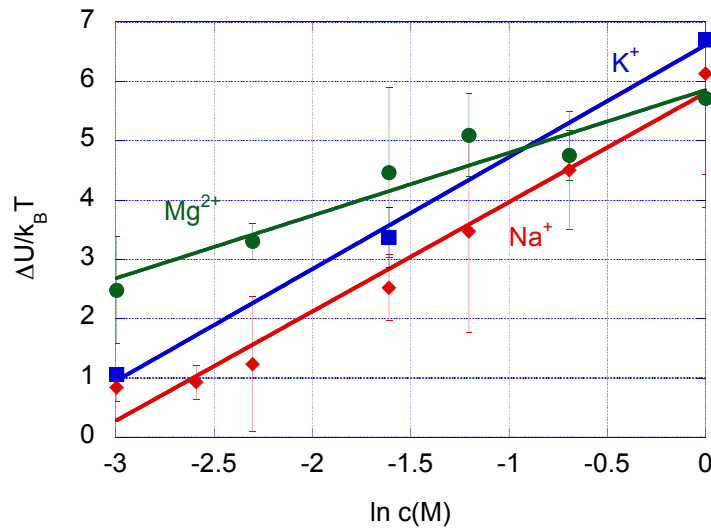

Fig. 6. Ionic contribution to the lowering of the energy barrier for egg-box unzipping, for two monovalent and a nominally non-binding divalent cation. ΔU is obtained from the measurement of the peak velocity jump following a ionic shock, as described in Baumberger & Ronsin (2010)[5]. Best fit slopes are 1.84 ± 0.14 (Na^+), 1.89 ± 0.11 (K^+), 1.06 ± 0.16 (Mg^{2+}).

Finally, we shall comment the relative position of the Mg^{2+} and Na^+ data. Keeping in mind that ΔU is defined with reference to a bare sodium alginate gel with a free counterion concentration c_0, the following relationships must hold:

$$\Delta U^{Na^+} = k_B T \ln\left(\frac{[Na^+]^2}{c_0^2}\right) \tag{9}$$

and

$$\Delta U^{Mg^{2+}} = k_B T \ln\left(\frac{[Mg^{2+}]}{c_0^2 R^3}\right) \tag{10}$$

where R^3 is a volume which appears here since we compare the kinetic constant of a second order exchange reaction ($Ca^{2+} \leftrightarrow Na^+$ in the reference state) with that of a first order one ($Ca^{2+} \leftrightarrow Mg^{2+}$). From the value of $[Mg^{2+}]$ extrapolated to $\Delta U = 0$ we obtain $R \simeq 1.6$ nm, a microscopic value which can be interpreted as the capture radius of a chelating cage (whose repetition length along the egg-box structure is 0.9 nm).

This confirms the simple picture in which ion exchange in the process zone of a crack in alginate gel is fully accounted for by a kinetic equation, the order of which is fixed by the electroneutrality requirement. The exchange rate is limited by the energy barrier for an opening event. The counterions which cooperate to this opening are those situated in the close vicinity of the cage, their contribution being merely entropic. This means that the binding energy of Mg^{2+} ions, if any, must remain smaller than the measured entropic shift, say on the order of $k_B T$, corresponding to transient bonds. This is compatible with the fact that the reported magnesium alginate "gels" are very weak, the tangent of the loss angle barely reaching unity [11],

5. Conclusion

We have confirmed the role of non-binding cations as accelerator of the fracture process in calcium cross-linked alginate gels. This effect, previously studied in details for Na^+, has been confirmed here for an other monovalent cation (K^+) and, more interestingly to the non-binding divalent one Mg^{2+}. This enabled us to estimate a capture radius for the ion exchange process, found on the order of the length of a chelating cage. This coherent picture led us to conclude that if Mg^{2+} have some affinity for alginate molecules, the corresponding binding energy must however remain of order $k_B T$.

The instant embrittlement induced by a ionic shock could hinder the use of alginate gels in physiological environments where structural integrity and load-bearing capacity are required. This however can be thought as a powerful analytic tool for studying the fracture mechanics of those ultra-tough, double network gels in which a ionic alginate network is the dissipative structure [4,12].

More generally, we would like to convey the idea that it is always judicious to "wet" the tip of a steady crack in a physical gel, either with the solvent itself [6] or with a liquid contrasting in viscosity [6,13] or salinity [5] with the bulk solvent. This proved a powerful experimental procedure to unravel the fracture mechanisms [6,5] and to get insight into the structure of the process zone [13].

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