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Emergence of Plasticity through Inter-Fibril Sliding in a Supramolecular Hydrogel.

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Abstract

Biological matter consists of complex networks of fibrillar assemblies that can withstand substantial mechanical stress without brittle fracture. Replicating these properties in synthetic materials - particularly the combination of strain stiffening and structural plasticity - has remained challenging without relying on covalent polymers or permanent chemical crosslinking. Here we report a purely supramolecular hydrogel that uniquely integrates both strain stiffening and structural plasticity, and we introduce a multiscale framework for studying plasticity in supramolecular materials. The material incorporates two orthogonal interaction modes, physical crosslinks that drive strain-stiffening behaviour, and inter-fibril sliding that enables plastic deformation without loss of elastic stiffness. This work reveals structural plasticity as an emergent and designable property of supramolecular networks, opening routes toward bioinspired, adaptive soft matter beyond the elastic regime.

Main

Unlike synthetic matter, biological tissues, such as the cytoskeleton or the extracellular matrix, demonstrate a remarkable ability to withstand mechanical stresses of varying intensities while retaining their dynamicity¹. This behaviour arises from the complex hydrogel network of supramolecular fibrillar assemblies, such as collagen, actin, vimentin, and keratin. The fibre networks make use of two sought-after non-linear mechanisms¹; namely, strain-stiffening²—an immediate enhancement in stiffness—and structural plasticity³—adapting local structure to intense mechanical load. Interestingly, while hydrogels are a massive field with over 15,000 published articles in 2024⁴; there is a distinct lack of studies that investigated design criteria for the incorporation of structural plasticity in a purely supramolecular hydrogel. The current state of the art predominantly relies on composite or dynamic covalent networks, commonly utilising covalent polymer networks and chemical crosslinking^{5,6}. Contrary to biological tissues, these strategies typically result in brittle fracture at high strain as opposed to ductile structural plasticity.

The challenge in designing supramolecular systems arises from their inherently complex and multistep assembly pathways, which are governed by a delicate balance of noncovalent interactions^{7,8}. In fibrillar systems, two orthogonal interaction types must be precisely designed and controlled: the intrafibrillar interactions that drive fibril formation, and the interfibrillar interactions that promote physical crosslinking and higher order fibre formation. Indeed, biological fibre monomers rely on this structural anisotropy to form these well-defined hierarchical structures.

We demonstrate that combining a physical crosslinking motif enabling inter-fibril sliding, with a rigid aromatic core that promotes fibril formation, allows for the design of mechanically-responsive hydrogel networks. By varying simple parameters such as salt concentration and temperature, these inherently structurally plastic networks can be tuned to modulate their strain-stiffening behaviour.

Supramolecular hydrogelator

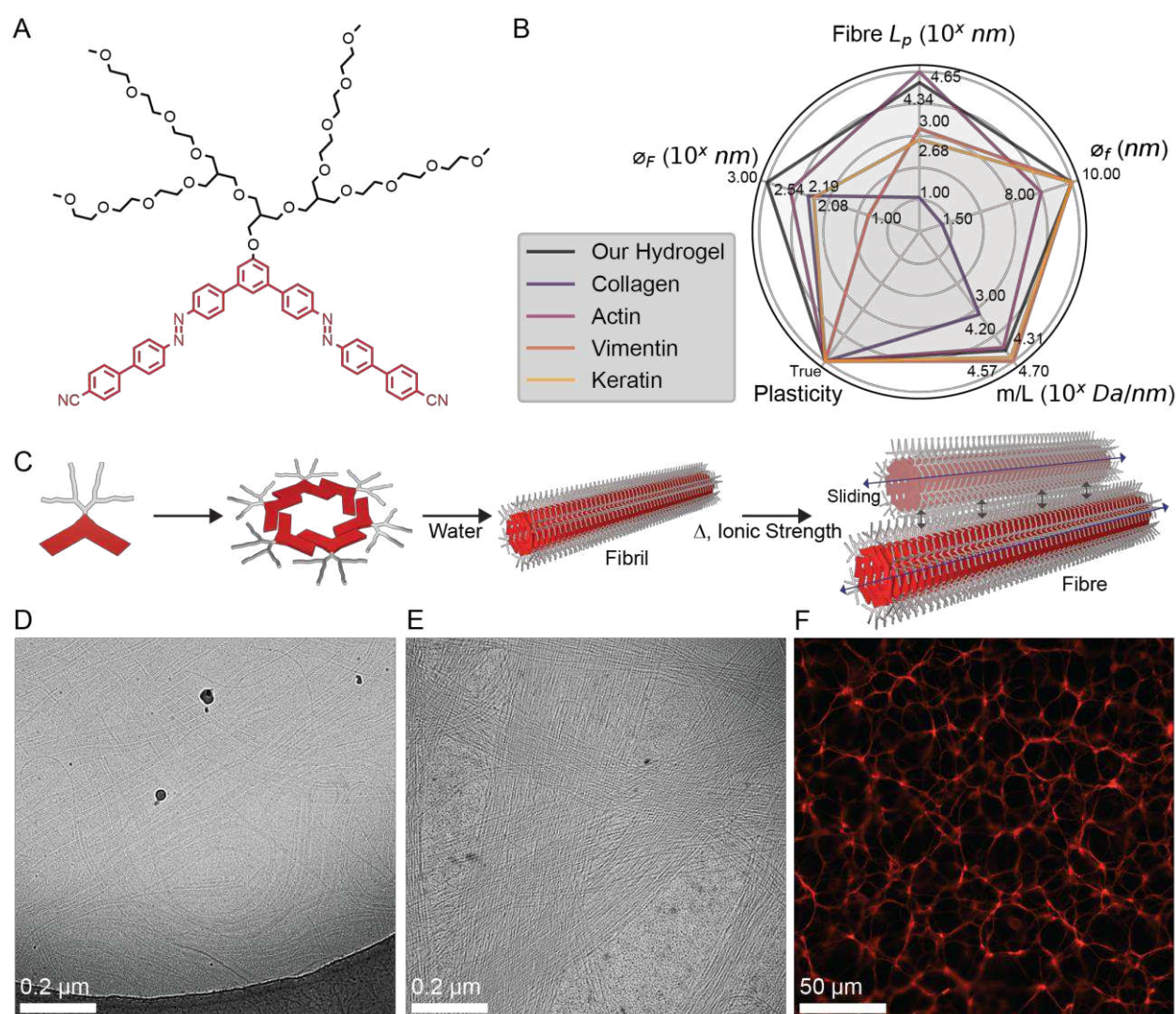


Fig. 1 Design of the single-component supramolecular hydrogel. (A) Molecular structure of the supramolecular hydrogelator. (B) Comparison of fibre diameter (θ_F), fibril diameter (θ_f), fibre persistence length (L_p), mass per unit length (m/L), and plasticity among our hydrogel, actin^{1,9-12}, keratin^{1,13-15}, vimentin^{1,16-19} and collagen^{1,20-23} fibres across various condition (Table S1). (C) Schematic of assembly process; single monomers combine to form hexameric slices that stack to form fibrils spontaneously in water. Influenced by salt, an LCST-transition can be triggered resulting in bundling of fibrils to form a percolated hydrogel network of fibres. (D) Cryo-EM micrograph of the fibrils pre-gelation (0.66 mM monomer, 1 M KCl). (E) Cryo-EM micrograph of the fibres (bundles of fibrils) composing our hydrogel (0.66 mM monomer, 1 M KCl, blotted at 40 °C). (F) Epi-fluorescent micrograph demonstrating the well-defined structure of our hydrogel (0.39 mM monomer, 1.1 M KCl, Nile-Red stained).

Our single building block²⁴ (Figure 1A) is capable of forming hydrogels with properties in line with prevalent biochemical fibrillar systems such as actin^{1,9-12}, keratin^{1,13-15}, vimentin^{1,16-19} and collagen^{1,20-23} based on mass per unit length ($m/L = 20.5 \text{ kg mol}^{-1} \text{ nm}^{-1}$), fibre persistence length ($L_p = 22 \text{ }\mu\text{m}$), fibril ($\theta_f = 12 \text{ nm}$) and fibre diameter ($\theta_F = 1 \text{ }\mu\text{m}$), and plasticity across various conditions (Figure 1B, Table S1). Its amphiphilic design consists of two distinct chemical moieties that provide complementary lateral interactions. Upon addition to water, the hydrophobic V-shaped aromatic core spontaneously directs the self-assembly, combining the hydrophobic effect, π - π interactions, and shape-recognition, to form a solution of micrometre-

long fibrils, consisting of hexameric slices, with an external diameter of 12 nm (Figure 1C and D)²⁴. The solubility, in turn, is ensured by outward-facing branched oligoethylene glycol (OEG) side-chains²⁴. Importantly, the incorporation of OEG sidechains allows for stimuli-responsive phase behaviour; namely, upon heating the sample, the OEG sidechains undergo a lower critical solution temperature (LCST) transition towards hydrophobic coils^{25,26}. Moreover, the LCST can be adjusted by the addition of potassium chloride (KCl) from 60 °C without KCl, to sub-ambient temperatures at 1.2 M KCl and above (Figure S1). The effects of this transition are threefold, demonstrating the versatility of OEG sidechains as a design feature. Firstly, the randomly oriented fibrils (Figure 1D) bundle to form thick fibres (Figure 1E and F). Secondly, these fibres are physically crosslinked to form a percolated hydrogel network as determined by cryogenic transmission electron microscopy (Cryo-TEM) (Figure S2), epifluorescence microscopy (Figure 1F) and bulk rheology (Figure S3). Thirdly, inter-fibril sliding can occur enabling structural plasticity (Figure 1C). The simple combination of monomer concentration and salt concentration enables control over the architecture and properties of the hydrogel, revealing novel structure property relationships.

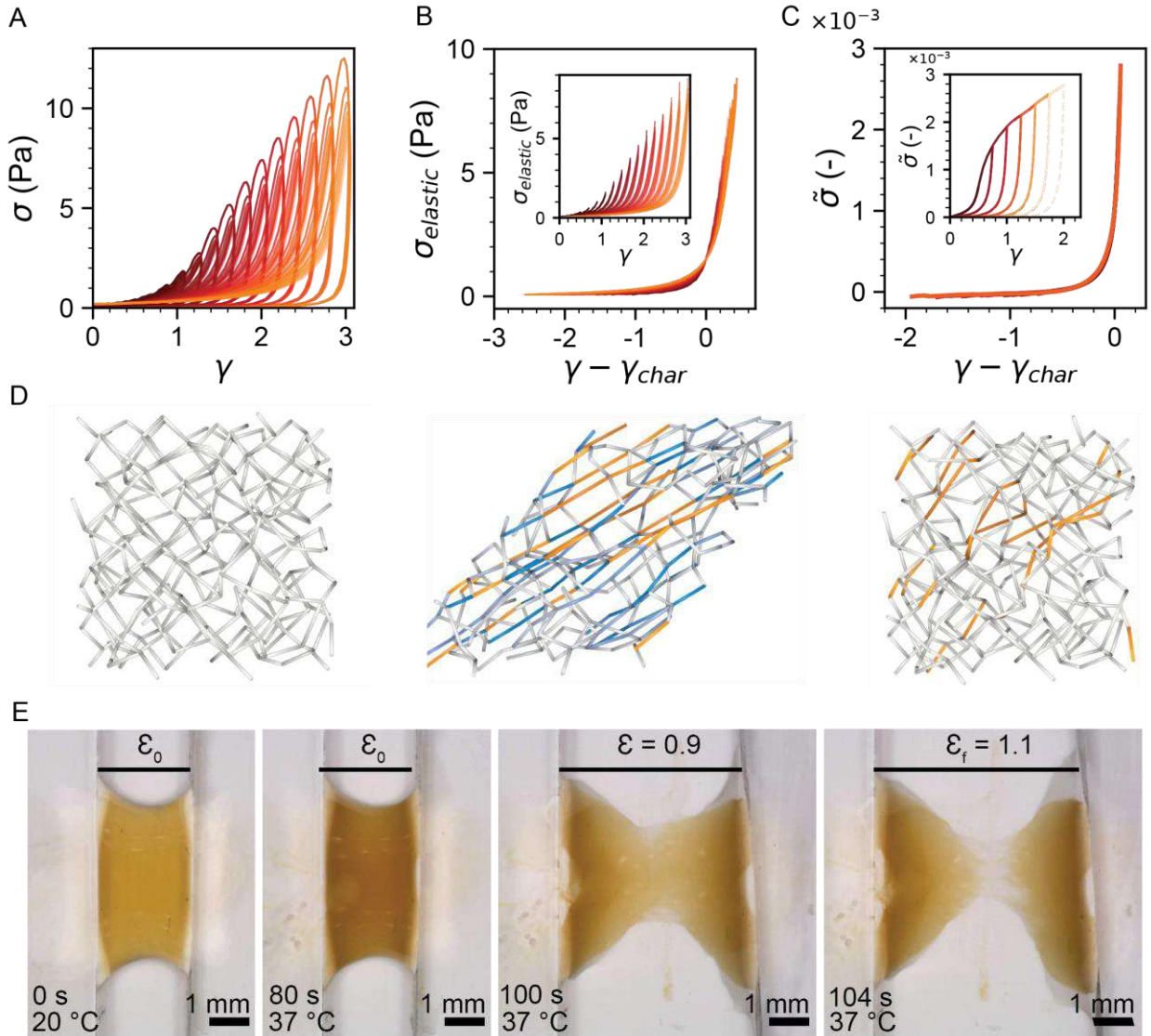


Fig. 2. Plasticity through inter-fibril sliding. (A) Experimental stepwise strain cycles (0.78 mM monomer, 1 M KCl). (B) *inset*: Elastic midlines calculated by averaging the observed stress in the forward and backward curve; *main*: Rescaled curves following the protocol proposed by Münster et al.²⁷ affirming hydrogel plasticity. (C) *inset*: Elastic response of the computational model assuming athermal and quasistatic conditions and a reduced bending rigidity $\tilde{\kappa} = 0.001$; *main*: Rescaling of the simulation data²⁷. (D) Snapshots of simulations for athermal fibre networks: the initial state (left) is deformed at a strain of 0.75 by elastic stretching (middle, blue) and lengthening (middle, orange); the deformation remains after removing the strain (right, orange). Note that only a handful of fibres bear most of the stress applied to the system. (E) Tensile testing of a hydrogel (3.33 mM monomer, 1 M KCl): the material was added in solution phase at 20 °C in between two glass slides on a PTFE surface, and after heating to 37 °C (indicated by the colour change) a tensile strain was applied. This demonstrates the material plastically adapting to at least 90% tensile strain (ϵ) before it slowly fractures at 110% strain (ϵ_f). Notably, some extending fibres can be observed at this high strain, and after fracturing the material retains its deformation instead of springing back elastically, *i.e.* stress has been relaxed plastically before fracturing (Movie S1).

The strain-stiffening and plastic response becomes apparent, when the hydrogel (0.78 mM monomer, 1 M KCl) is subjected to stepwise sinusoidal strain cycling in a shear rheometer²⁷ with an increasing strain amplitude every 10 cycles. This measurement yields Lissajous curves

(Figure 2A) that appear as loops due to combined elastic and viscous effects. Since the deformation profile is symmetric the elastic response is extracted by averaging the forward and backward curve, obtaining the elastic midlines in fig. 2B (inset)²⁷. We find that these elastic midlines can be rescaled to form a master curve (Figure 2B) by shifting each curve by γ_{char} - the strain at which the stress is equal to 1.5 Pa, *i.e.* the inflection point in the stress strain behaviour. Following the argumentation of Münster *et al.*²⁷, this behaviour reveals that our artificial hydrogel exhibits structural plasticity, much like its biological counterparts. Interestingly, the plasticity does not result in weakening of the sample, but rather shifts the elastic response towards higher strain. This indicates that the microscopic mechanism behind the *elasticity* remains the same from the start to the end of the experiment²⁷, despite the progressive plastic deformation and significant energy dissipation. Literature on biopolymer networks²⁷ and colloidal gels²⁸ typically attributes the shifted elastic response and plasticity to lengthening at the fibre level.

We investigate how this fibre-level effect changes the macroscopic mechanical response using a coarse-grained computational model that was developed to understand how network-level deformations in stiff biopolymer networks affect their elastic response²⁹⁻³¹ as well as their plasticity and fracture³. The model assumes quasi-static deformation and is based on a 3D fibre network created by diluting and distorting a diamond lattice (Figure 2C and D). When a shear deformation is applied to this network, it will initially deform non-affinely, resulting in the bending of fibres. However, at a certain point, some fibres will align in the direction of the applied strain such that they are stretched out. In the model, the fibres are deformed plastically by lengthening if their relative elongation exceeds a given yield strain (ϵ_y). Tensile stress can be removed from the fibres by returning to the zero-strain point, but the lengthening remains (Figure 2D). Additionally, the analysis of simulation snapshots demonstrates that the stress is not dissipated uniformly throughout the network. Rather, only a fraction of the fibres carries the majority of the stress and these fibres undergo plastic elongation. Since the model only captures the elastic component of the stress response, it should be compared to fig. 2B. However, not only does the model qualitatively match the experimental stress-strain response of the material (Figure 2C inset), it is possible to apply the same rescaling procedure²⁷ to form a master curve (Figure 2C).

We set out to validate these local effects—fibre alignment, the presence of stress-bearing fibres, and plastic deformation—using a tensile testing experiment. A hydrogel (3.3 mM monomer, 1 M KCl) was prepared with a storage modulus comparable to that of brain tissue³² and was added in a solution phase between two glass slides resting on a PTFE surface. Gelation was induced by heating the setup to 37 °C, as indicated by the colour change in Fig. 2E. The material was then subjected to tensile strain by slowly separating the two glass slides. Interestingly, we find that the hydrogel can plastically accommodate strains of approximately 90% before fracturing. Notably, when fracture occurs at ~110% strain, the material does not recoil, indicating substantial stress dissipation through plastic deformation that dominates over elastic recovery (Figure 2E). Moreover, during fracture we observe fibres aligned with the tensile direction protruding from the two fractured halves, consistent with stress-bearing fibres (Movie S1).

161 Inter-fibril sliding as a plasticity mechanism

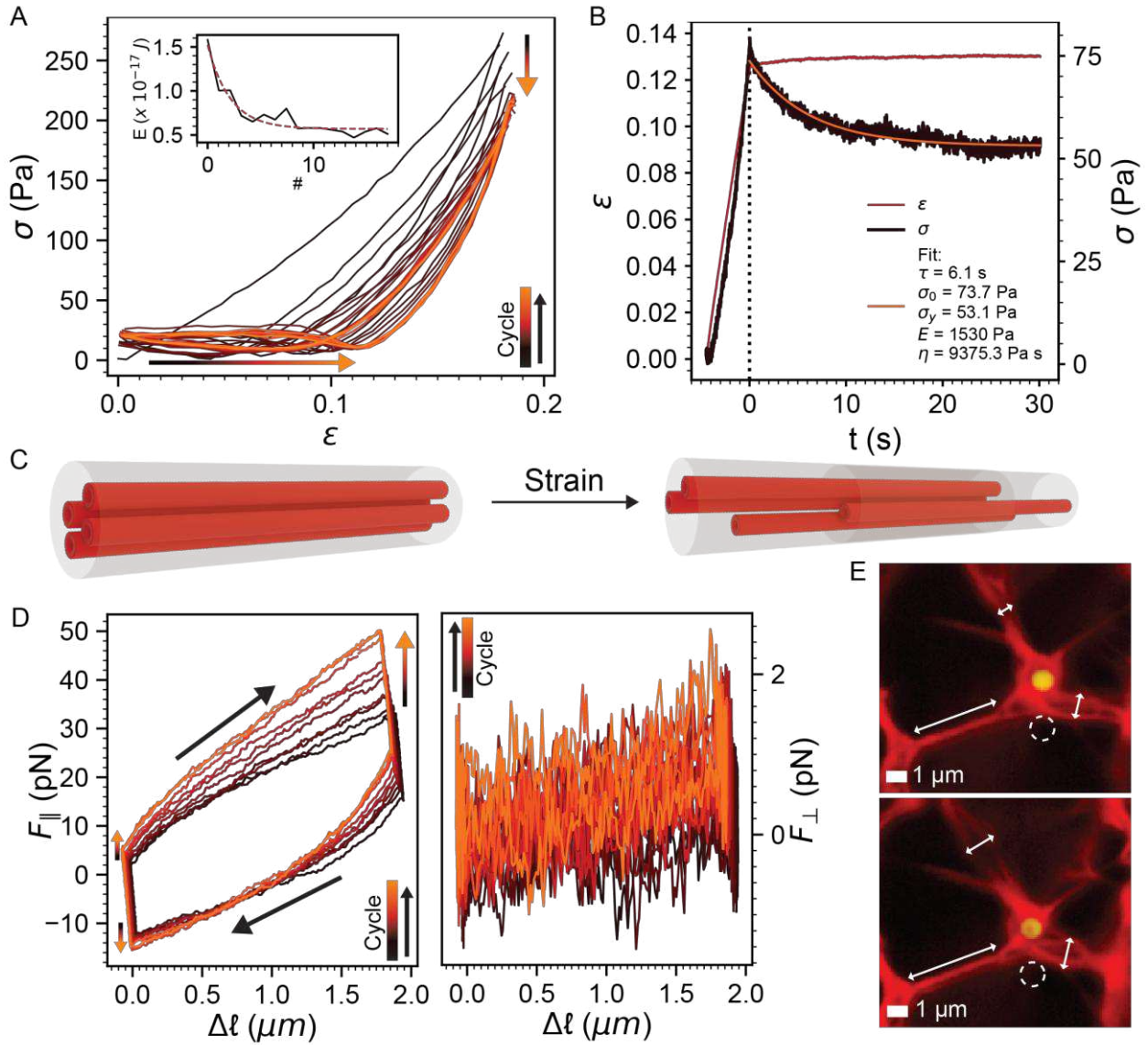


Fig. 3. Evidence of inter-fibril sliding by Optical Tweezers micro-rheology. (A) *main*: Cyclic-loading on a single fibre (0.66 mM monomer, 1 M KCl, 37 °C) affirming that plasticity occurs locally; *inset*: Energy dissipation indicates the material adapts. (B) A single fibre (0.66 mM monomer, 1 M KCl, 37 °C) being kept at a fixed strain (ϵ), relaxing its tensile stress (σ) through lengthening; this indicates that inter-fibril sliding occurs on the 7 ± 2 s timescale (τ) with a yield-stress (σ_y) of 53 Pa, a Young's modulus E of 1530 Pa and a sliding viscosity of 9375 Pa s. (C) Schematic of the inter-fibril sliding mechanism for hydrogel plasticity; under applied strain a fibre's constituent fibrils slide to relax the accompanying stress. (D) Cyclic loading protocol applied to piece of hydrogel (0.66 mM monomer, 1 M KCl, 37 °C) with a 30 wait-time in between elongational and compressive strokes; the flat edges indicate force-relaxation through local lengthening and shortening on the elongational and compressive strokes respectively, and the increase of force at similar strain (Δl) as a function of cycle reveals an enhanced elastic response. The force is measured at the stationary trap in the parallel and tangent direction to the applied force at the moving trap. (E) Confocal micrographs of a gel (0.5 mM monomer, 1 M KCl, 37 °C, DBCO-Cy5 labelled) before (top) and after (bottom) point-stress deformation by repeatedly turning on and off the optical trapping laser (dotted circle), arrows indicate the different types of local deformation modes observed: splitting and elongation.

We hypothesize that the plastic response of our hydrogel arises from fibre lengthening due to inter-fibril sliding. To that end, we set out to analyse stress-bearing fibres during the deformation process as opposed to after fracturing. A hydrogel sample (0.66 mM monomer, 1 M KCl, 37 °C) was prepared and subsequently broken down using minimal mechanical agitation for micro-rheological analysis using optical tweezers. Freely diffusing fibres were attached to optically trapped 1 μ m amine-coated fluorescent polystyrene beads. Strong multivalent hydrogen bonding between the OEG chains and amino groups ensures stable adhesion ($F \sim$ nN)³³. This enables us to perform repeated extension-compression cycles, without bead detachment, referred to as cyclic-loading^{34,35}. In a typical experiment, one of the optical traps is moved to a pre-specified strain and back while the forces/stresses in the parallel (fibre axis) and tangent direction on both optical traps are recorded. By applying these cyclic-loads in series, one can gain information about the material properties of the fibre as a function of time and sample history (Figure 3A, Movie S2).

Indeed, we find that the fibre plastically extends upon successive strain cycles as the zero-stress length of the material is shifted towards higher strains (Figure 3A), and sequentially less force and energy is required to apply the same amount of strain (Figure 3A). Since the fibre is in isolation (*i.e.* no network dynamics), and the monomer exchange process is limited in aqueous media²⁴, inter-fibril sliding is the only accessible mechanism for fibre lengthening (Figure 3C). Interestingly, the Young's modulus of the material is not only retained, it actually seems to increase with the number of oscillation cycles (1530 Pa to 2200 Pa), judging by the slope of the stress strain curve upon the elongational stroke (Figure 3A and S4). Combining insights with the network simulation snapshots (Figure 2D) suggests that upon each subsequent fibrillar shift, more of the constituent fibrils are aligned; thereby increasing the Young's modulus. Lastly, by incorporating a 30-second relaxation period between the tensile and compressive strokes, the timescale of inter-fibril sliding was investigated. It was found that a single fibre is capable of relaxing its tensile stress, and this process is characterized by a yield strain (ϵ_y) of ~ 0.03 and a sliding timescale of $\tau = 7 \pm 2$ s (Figure 3B and S5). Additionally, the material exhibits compressional plasticity on the same timescale, relaxing stress by shortening its contour length (Figure S5), albeit to a lesser extent than in elongational plasticity. We attribute this behaviour to a competition between inter-fibril sliding and buckling. Based on the stress-strain curves (Figure 3A) and correlated brightfield microscopy (Figure S6), it was observed that with successive cyclic loads, the material increasingly buckles during each compression cycle to accommodate the length-increase.

We focus next on an intact sample of hydrogel (0.66 mM monomer, 1 M KCl, 37 °C). A 30-second wait time was applied between the constant-rate elongational and compressive strokes^{34,35} that allows us to quantify the force-relaxation and propagation in the network. Two pre-calibrated beads are embedded in the network. One bead is actuated according to the described wave pattern, while the force is measured at the stationary bead. The results show that the force applied to the bead effectively propagates through the network while retaining directionality, with the majority of the force being transmitted in the parallel direction rather than the tangential one (Figure 3D). Notably, the hydrogel sample exhibits plasticity on the same timescale as the single fibre, supporting inter-fibril sliding as the underlying mechanism for both elongational and compressive strokes (Figure 3D, Figure S7 and Movie S3). However, much like in shear rheology, it remains difficult to determine which specific fibres undergo this lengthening or shifting process. Moreover, repeated application of point-stress to the network reveals that the material exhibits an enhanced elastic response as a function of strain history, attributed to network alignment—*i.e.*, higher stress at similar strain after additional cycles. (Figure 3D, Figure S8 and Movie S4). Indeed, confocal microscopy reveals that by incrementally pulling on a polystyrene bead incorporated in a network node (0.5 mM monomer, 1 M KCl, 37 °C),

anisotropic deformations of the local network can be observed (Figure 3E). Some fibres elongate, while others appear to split into smaller ones, indicating that local reorganization of fibrils within a fibre—via inter-fibril sliding and bending—is possible while preserving the hydrogel's overall integrity and connectivity (Figure 3E). Crucially, a purely affine deformation model based on the extracted fibre properties fails to capture the observed macroscopic response—for example, the strain-stiffening behaviour is absent in single fibres—indicating that non-affine deformations play a significant role. In fact, only a fraction of the fibres contributes to the elastic and plastic response.

Hydrogel morphology and versatility

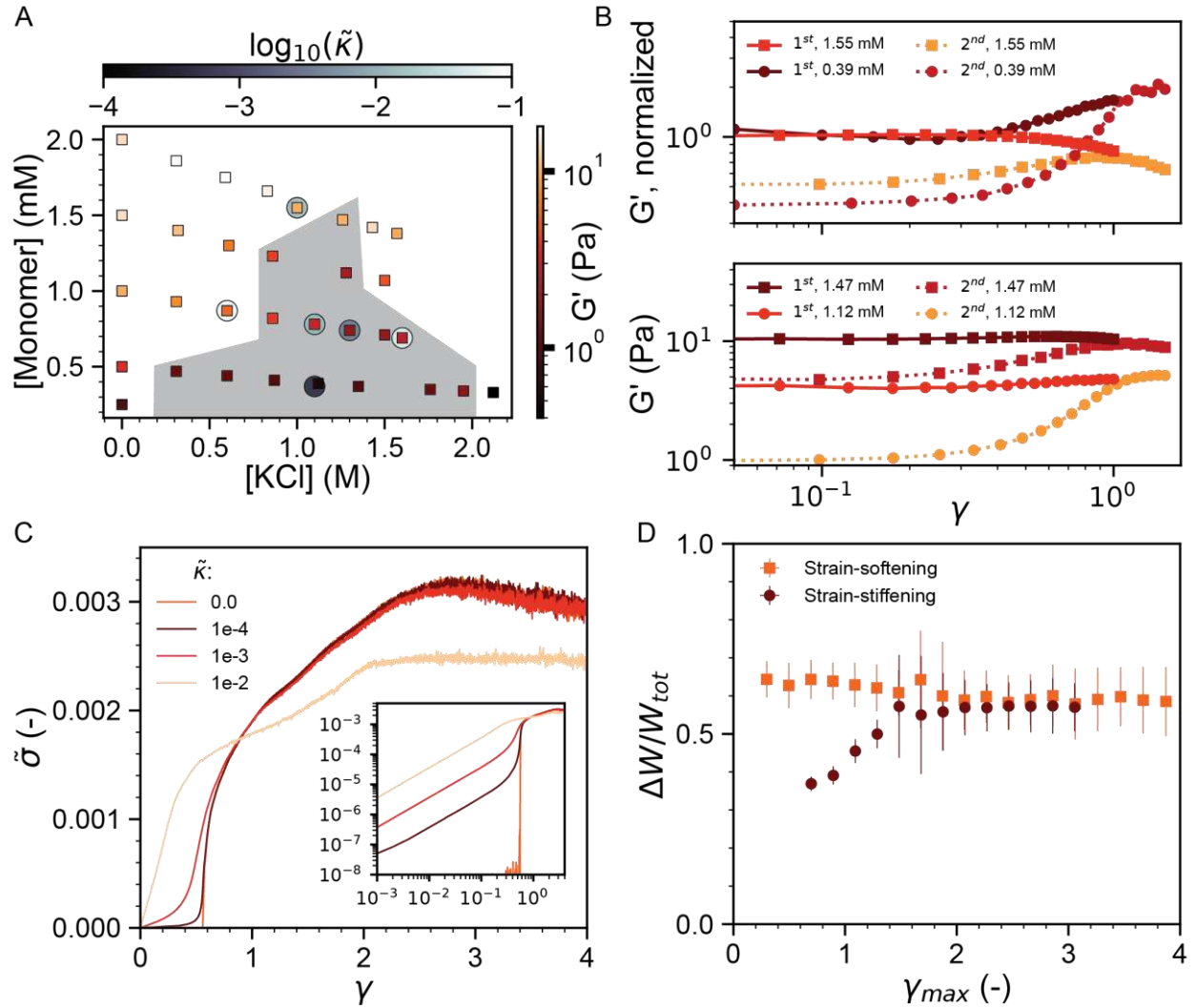


Figure 4. Controlling network morphology and mechanics. (A) Hydrogel phase diagram as a function of monomer and KCl concentrations. The grey area denotes the parameter space inside which strain-stiffening occurs on the first sweep. The orange colormap (squares) indicates the linear (low-strain) modulus (G'), the grey-blue colormap (circles) indicates the reduced bending rigidity ($\tilde{\kappa}$). (B) Mechanical response of hydrogels to successive strain sweeps; top: Difference of behaviour between monomer concentrations at 1 M KCl. Strain-stiffening on the first sweep is present at 0.39 mM but obfuscated by plasticity at 1.55 mM. After being plastically deformed all networks undergo a mechanical transition and strain-stiffening becomes more pronounced. Bottom: Mechanical training of a higher-concentration gel (1.47 mM Monomer, 1.2 M KCl) with a preliminary sweep makes it possible to obtain the same initial modulus as a lower-concentration hydrogel (1.12 mM Monomer, 1.2 M KCl). However,

the strain-stiffening ability is enhanced. **(C)** Simulated stress-strain curves for different $\tilde{\kappa}$. At low $\tilde{\kappa}$ the plastic response is identical to a network without bending ($\tilde{\kappa} = 0$), and does not affect the strain-stiffening behaviour. However, when $\tilde{\kappa}$ approaches 10^{-2} a coupling arises between $\tilde{\kappa}$ and the plasticity threshold λ_p , and the strain-stiffening response is obfuscated by plasticity induced softening. **(D)** Comparing strain-stiffening and a strain-softening network by calculating the fraction of dissipated work with respect to the total amount of work for each cycle (Figure S9), revealing a clear difference in the onset of plasticity.

As the network morphology mediates the hydrogel's macroscopic response, we aim to directly control the degree of strain-stiffening using two key parameters: the monomer concentration, which affects the fibril volume fraction, and the KCl concentration, which dictates the transition temperature for network formation. In fact, the solution-gel transition temperature (*i.e.* LCST) is independent of the monomer concentration and decreases with an increase in KCl concentration (Figure S1). This latter observation is in line with previously reported experimental²⁵ and theoretical²⁶ works on phase separation of OEG, and is caused by a competition between hydration of the potassium ions and the polyethylene glycol chains, which eventually coil and expel water.

The influence of morphology on the mechanical properties is discussed using combined insights from biopolymer theory and our computational model for network plasticity. The linear modulus and the extent of the strain-stiffening response depend strongly on the reduced bending rigidity $\tilde{\kappa} = (\kappa / \mu) / L_0^2$ with L_0 being the average distance between crosslinks, and μ and κ the respective stretching and bending moduli of the fibres in the network. Assuming that the fibres in our system behave as continuous elastic rods, and that L_0 is comparable to the mesh size, this parameter can be estimated as $\tilde{\kappa} = \frac{1}{16} D_b^2 / L_0^2$, with D_b being the fibre diameter²⁷. It should be noted that for fibres, the expression for $\tilde{\kappa}$ depends on the strength of the interaction between fibrils as well³⁶. Nevertheless, both in the limit of weak and strong interactions, similar trends in $\tilde{\kappa}$ are observed (Supplementary Text - Expressions for $\tilde{\kappa}$ of fibres).

From the epifluorescence micrographs we can extract $\tilde{\kappa}$ for different gelation conditions by measuring L_0 and D_b and find that the morphology of the networks is highly dependent on monomer and KCl concentrations (Table S2, Figure S10). In accordance with literature²⁷, and in line with theories on gelation kinetics³⁷⁻⁴¹, $\tilde{\kappa}$ increases with monomer concentration (Table S2, Figure S10). A theoretical model proposed by Sengab and Picu⁴² provides an in-depth investigation of non-crosslinked networks with inter-fibre adhesion, such as our hydrogel networks. This framework describes the interplay between fibre volume fraction, inter-fibre adhesion, fibre length, and fibre bending stiffness⁴³. In the case of our hydrogel, low monomer concentrations place the resulting network in the “cellular” domain, which describes networks with large mesh size and thick fibres^{42,44}. However, at similar concentrations of KCl, higher monomer concentrations bring the network towards the “fibrous” domain, where individual fibres are locked in place, yielding a denser network of thin fibres. Interestingly, as a function of KCl concentration, we observe a minimum $\tilde{\kappa}$ at intermediate concentrations (*i.e.* coarse cellular structure as opposed to fine fibrous structure). We attribute this to a balance between the rate of fibrillar encounters, and the timescale of fibrillar alignment into fibres. Both of these properties are influenced by temperature⁴⁵.

Moreover, we can plot the linear storage modulus according to monomer concentration and KCl concentration in a phase diagram, and map an area in this parameter space where the hydrogels strain-stiffen upon their first deformation (Figure 4A), as well as point out the value of $\tilde{\kappa}$ in characteristic regions of the phase diagram. This area, highlighted in grey, is characterized by very soft networks with linear storage moduli ranging from 0.2 Pa up to 10 Pa. Outside of this region, networks don't have a visible strain-stiffening response upon the first

strain sweep; however, a second sweep reveals their strain-stiffening ability (Figure 4B-*top*). Strikingly, this initial absence of strain-stiffening coincides with higher values of $\tilde{\kappa}$, and a more fibrous, as opposed to cellular, architecture (Figure S10). Based on the optical tweezers experiments we determined the yield strain ϵ_y of a single fibre to be $\sim 3\%$; this can explain the strain-softening behaviour of the fibrous networks. Indeed, if we use a very low plasticity threshold in our model (1% strain, lower due to expected polydispersity in the sample), we observe this shift from strain-stiffening towards strain-softening when moving from a low- $\tilde{\kappa}$ network to a high- $\tilde{\kappa}$ network (Figure 4C and S11-*left*). This shift is caused by the earlier onset of plasticity at high $\tilde{\kappa}$, forced by a higher resistance to bending. This behaviour is similar to what we observe experimentally (Figure S11-*right*). We extracted the dissipated work by plastic effects from the strain sweep experiments (Figure 4D and S9), and find that plastic effects, indeed, start to dominate the mechanical response at significantly lower strains for high- $\tilde{\kappa}$ networks.

Additionally, this effect provides an explanation for the trends observed in the modulus-strain plots of the experimental mechanical response (Figure 4B). Because plasticity happens earlier in the high- $\tilde{\kappa}$ network, it completely obfuscates the strain-stiffening response, which is why some networks do not initially demonstrate strain-stiffening. Upon subsequent deformations, further plastic effects such as lengthening are negligible, as long as $\gamma_{\max}$ is not exceeded, such that the strain-stiffening becomes apparent. At large deformations, however, we also expect other contributions, such as anisotropic fibre alignment⁴⁶ or strain-induced fibre bundling promoted by the higher line density.

Evidently, the structure and behaviour of the material can be adapted substantially using simple parameters, making it suitable for tuning towards a variety of applications^{47,48}. For example, training a high-concentration sample lowers its modulus to the level of a lower-concentration sample, but gives it a strong strain-stiffening ability (Figure 4B-*bottom*). This results in a material with similar mechanics at usual conditions while surviving higher stresses if the need arises due to a 100% stiffness increase at high strain. In connection to a primary function of the extracellular matrix, the control over these properties is critical for determining cell differentiation pathways⁴⁹ and the inherent structural plasticity is crucial for the development of cell cultures⁵⁰.

Discussion

Using a hierarchically self-assembling monomer as a building block, we were able to synthesise an artificial hydrogel displaying combined structural plasticity and strain-stiffening. These two emergent behaviours are both critical biomaterial properties that work in tandem to protect against high mechanical stresses. While strong hydrophobic and π - π interactions ensure the integrity of the elementary fibrillar building blocks in water, weaker, temperature-controlled OEG-OEG interactions enable bundling and crosslinking, and underlie the inter-fibril sliding mechanism responsible for plasticity. By adjusting monomer and salt concentrations, we can tune the balance between the two interaction modes, yielding a wide variety of network morphologies and mechanical properties.

From a material design perspective, integrating inter-fibril sliding motifs emerges as a promising strategy, offering precise control over plasticity and enabling the rational design of biomimetic materials that extend beyond the purely elastic regime. This mechanical tunability is further supported by predictive modelling tools and by single-molecule techniques such as optical tweezers, which provide microscale insight. We anticipate that this behaviour is more general and will be observed in other synthetic supramolecular systems. Our novel

methodological framework, combining consistent experimental insights at both the network and individual fibre levels, accompanied by a model, can be adopted for future studies on plasticity in supramolecular systems. Overall, this research advances our understanding of structure–function relationships in adaptive materials and equips supramolecular chemists with new tools for the bottom-up synthesis and characterization of biocompatible, biomimetic systems.

Methods

Synthesis and characterization of compounds. The monomer was prepared according to the previously reported procedure²⁴. Detailed synthetic procedure for the preparation of compound AzO-N₃ is given in the Supplementary Information. Detailed procedure for the preparation of co-polymers with the monomer was previously reported⁵¹.

Sample preparation. The desired amount of monomer “paste” was transferred into a small vial and spread as much as possible against the vial’s interior wall. The desired amount of water was then added and the solution was gently vortexed at minimal speed settings (between 0 and 1) on a Scientific Industries Vortex-Genie 2, until the paste was completely dissolved. The obtained orange solution was left to rest overnight. An amount of saturated KCl (BOOM Laboratoriumleverancier) solution in water was then added to obtain the desired KCl concentration in the final solution. The solution was used the same day.

Cryo-TEM. 3 μ L of sample were deposited onto a quantifoil 3.5/1 holy carbon coated grid in a FEI Vitrobot. The environmental control system was set to a temperature about 2°C above the sample gelation temperature and a humidity of 100% to prevent evaporation. After 3 minutes, the sample was blotted and immediately plunge-frozen in liquid ethane. The images were recorded on a Tecnai T20 electron microscope operating at 200 keV using a Gatan model 626 cryo-stage. Images were recorded under low-dose conditions with a slow scan CCD camera and analysed using ImageJ.

Epifluorescence microscopy. To obtain red fluorescent networks, a few grains of Nile Red (< 0.1 mg) were added to the vial as a preliminary step to sample preparation. Acetone was added, then left to evaporate to obtain an even coating of the vial. Monomer “paste” was added to the vial and sample preparation was continued as described above. A well was created by attaching to a glass slide a piece of double-sided ThorLabs optically clear adhesive tape (50 μ m thickness) with a hole in its centre. Sample was deposited in the well and a coverslip (Electron Microscopy Sciences) was delicately added on top to avoid bubble formation and expel excess liquid. The sample was then heated to trigger gelation, using a Mettler-Toledo HS82 Hot Stage and its associated HS1 Hot Stage Controller. Fluorescence was observed on a Nikon Eclipse LV100N illuminated by a Nikon Intensilight C-HGFI. The white light went through the associated filter cube for green excitation and red emission (MBE45504, EX 510-560 nm, DM 575 nm and BA 580 nm). Images were recorded using NIS-Elements D Imaging Software and analysed using ImageJ. *Connectivity:* Network connectivity is defined as the average number of fibres joining into a node. For each visible node in the epifluorescence image the number of connections was noted and an average was made to yield the overall connectivity.

Optical tweezers. *Experimental set-up:* All experiments were conducted on a Lumicks C-Trap, with acquisitions on the Lumicks Bluelake software. The trap stiffness was calibrated

using the power spectrum density analysis (or thermal noise) method (Scanary v. 3.3.0, Lumicks). To assess the range of trap stiffnesses where it is possible to manipulate the sample without observing radiation damage, the trapping laser was focused on a fibre and the intensity was gradually increased, imaging the sample with a confocal fluorescence scan every 30 seconds of exposure (SI Figure 12). No appreciable radiation damage was observed with 10% of the laser power (5 μ W).

Network Deformation for Confocal Analysis: A sample of monomer was dissolved in acetonitrile together with Azo-N₃ (see Supplementary Information for synthesis and characterization) in a 50:1 molar ratio. The solvent was evaporated and the resulting paste was dissolved in water at a concentration of 5 mM. The sample was left to equilibrate overnight. The next day, 0.9 equivalent (with respect to Azo-N₃) of DBCO-Cy5 (Sigma-Aldrich, used without further purification) was added to the solution and left for at least 1 hour. Subsequently, the solution was diluted and KCl was added until the final concentrations were 0.5 mM in monomer and 1 M in KCl. This solution was pre-incubated with 1 μ m diameter amino-functionalized polystyrene beads (amine-modified polystyrene fluorescent red/orange, Sigma-Aldrich). Upon heating to 37°C these beads are incorporated in the cellular gel network. Bead-hydrogel dissociation was never observed, since the optical traps are unable to provide enough force at the used laser-powers. The hydrogel deformation was performed using 10% of the laser power (trap stiffness $k = 0.39$ pN/nm). The optical trap was switched off and positioned at ~ 1 μ m distance from the bead centre along the x direction. The laser power is ramped to 10% and the bead experiences a force field generated by radiation pressure. In response to that stimulation, network is progressively attracted towards the centre of the force field. This stimulation was repeated five times with a relaxation time of a couple seconds. Subsequently, the material was analysed using confocal microscopy at a wavelength of 638 nm and a power between 1 – 50 μ W to reveal anisotropic deformation of the network surrounding the bead (Figure 3e).

Single Fibre and Gel measurements: A sample of monomer was dissolved in acetonitrile together with Azo-N₃ (see Supplementary Information for synthesis and characterization) in a 50:1 molar ratio. The solvent was evaporated and the resulting paste was dissolved in water at a concentration of 1 mM and left to equilibrate in the dark overnight. Subsequently, 0.9 molar equivalents to Azo-N₃ of DBCO-Cy5 is added and equilibrated for at least one hour, diluted with aqueous KCl (3 M Stock) and heated to form a gel ([monomer] = 0.66 mM; [KCl] = 1 M, $T = 37$ °C) using a water-bath; subsequently, 1 μ L of the set gel was pipetted into 99 μ L of 0.2 μ m filtered 1 M aqueous KCl at 37 °C. The obtained solution was mechanically agitated by swiping it across an Eppendorf tube rack five times (vortexing and sonication provided too much mechanical agitation) and kept at 37 °C in a water-bath to obtain loose fibres and loose pieces of gel in solution. A custom hand-prepared three-zone microchip is loaded sequentially, with 1 μ m amino-functionalised polystyrene beads (amine-modified polystyrene fluorescent red, Sigma-Aldrich) in filtered 1 M aq. KCl, with 0.2 μ m filtered 1 M aq. KCl, and with the fibre solution. In the optical tweezer setup, pre-equilibrated at 37 °C for thermal stability of the force read-out, two beads are trapped optically and the force is calibrated at 10% laser power. Subsequently, the two beads are attached non-covalently to the ends of a fibre or piece of gel and moved to the clean 1 M aqueous KCl channel. Thereafter, the optical traps are moved to obtain a minimum in the force and tared. Furthermore, the trap distance is calibrated and

recorded using the piezo tracking of the lasers and an oscillatory elongational strain (1 $\mu\text{m/s}$ strain-rate, 2 μm amplitude) is applied to the fibres while recording the force/stress at the stationary trap. Alternatively, in the stress-relaxation experiments, a pause in the cycles is applied of 30s to determine the timescale of stress/force relaxation and to exclude non-relaxed components of the material's viscoelastic behaviour. Due to the material exhibiting buckling on the return stroke, thereby changing the angle of the force vector $\vec{F}$ relative to the deformation vector $\vec{x}$, the force magnitude ($\sqrt{F_{2,x}^2 + F_{2,y}^2}$) at the stationary trap is used for data analysis. The area in the force-distance curves where $F_{\text{extension}} > F_{\text{compression}}$ is defined as the dissipated energy during the cyclic loading (Figure 3a *inset*) and fitted with an exponential decay for illustrative purposes. Furthermore, in the case of the stress-relaxation experiment the exponential decay is fitted using the Maxwell model (Figure 3b, SI Figure 5 and 8).

$$\sigma(t) = (\sigma_0 - \sigma_y) \exp\left(\frac{-t}{\tau}\right) + \sigma_y$$

With:

$$\tau = \frac{\eta}{E}$$

Rheology. All experiments were conducted on a TA Instruments Discovery HR-3 equipped with a Peltier bottom plate and a 20 mm stainless steel crosshatched plate with solvent trap as top plate, to prevent evaporation and slipping as much as possible. 200 μL of sample were added to the bottom plate at room temperature, and the gap was set to 300 μm . The solvent trap was filled with water and droplets were also deposited on the Peltier plate to maximize humidity during the experiment. Gelation was achieved by a 2 $^{\circ}\text{C}/\text{min}$ temperature ramp, with a final temperature around 2 $^{\circ}\text{C}$ above gelation, and a 1 rad/s oscillation frequency. The various experiments were then performed at that same temperature and frequency. For multiple strain sweep experiments, an additional “backwards” strain sweep was performed in between the displayed sweeps, but was omitted for clarity.

Computational model. A model was employed to investigate the plastic response of the material, where fibres are already under significant stress and thermal fluctuations can be expected to be comparatively small. Therefore, we model the hydrogel networks as sub isostatic elastic networks under athermal conditions. Each network is generated from a diamond lattice of $N_x \times N_y \times N_z$ unit cells with dimensionless lattice spacing d , where all nearest neighbours are connected by bonds such that the connectivity at each node, i.e., the number of bonds connected to a node, is equal to the maximum connectivity $z_{\text{max}} = 4$, and each bond has an initial length $l = d$. Note that the size of the unit cells is set at $4d/\sqrt{3}$ to satisfy this condition, such that the box-size $L = \frac{4d}{\sqrt{3}}N$. Subsequently, the nodes are displaced in a random direction over a distance dr from their initial position; dr is picked randomly from a uniform distribution between 0 and dr_{max} . These networks are diluted by randomly removing bonds until a fraction p of initial bonds remain, such that the average connectivity becomes $\langle z \rangle = p z_{\text{max}}$. For these simulations we considered networks with an average connectivity $\langle z \rangle = 3.4$. The network resist both stretching and bending, such that the total energy of the system is given by

$$E = E_{stretch}^{fibre} + E_{bend}^{fibre} = \sum_{\langle ij \rangle} \frac{1}{2} \frac{\mu}{l_{0,ij}} (l_{ij} - l_{0,ij})^2 + \sum_{\langle ijk \rangle} \frac{\kappa}{l_{0,ij} + l_{0,jk}} (\theta_{ijk} - \theta_{0,ijk})^2. \quad (1)$$

Here $E_{stretch}^{fibre}$ is the total stretching energy, which is the sum over all bonds of which the connected nodes are indicated with set of indices $\langle ij \rangle$. For each bond the stretching energy is a function of the stretching modulus μ , the distance between nodes l_{ij} , and the rest length $l_{0,ij}$. E_{bend}^{fibre} is the total bending energy, which is the sum over the all angles between bonds connected to the triplet of nodes $\langle ijk \rangle$. For each triplet the bending energy is a function of the bending modulus κ , the rest lengths of the two bonds in the triplet, $l_{0,ij}$ and $l_{0,jk}$, the current angle θ_{ijk} between these bonds, and the corresponding rest angle $\theta_{0,ijk}$. We express these quantities in terms of the lattice spacing d and the stretching constant μ , providing us with the unitless quantities $\tilde{l} = \frac{l}{d}$, $\tilde{\mu} = \frac{\mu}{\mu} = 1$, and $\tilde{\kappa} = \frac{\kappa}{\mu d^2}$.

The elastic response of this network is obtained by applying an affine shear deformation to the network with Lees-Edwards boundary conditions along the y-direction and periodic boundary conditions along the x- and z-axis, followed by minimization of the energy of the system through the FIRE algorithm until the root mean square force on the nodes is lower than F_{rms} ⁵². A virtual mass of the nodes in the networks is computed as $m_i = \frac{1}{N_{ij}} \sum_{\langle ij \rangle} \frac{\mu_{ij}}{l_{0,ij}}$. Next to the recommended settings in ref.⁵² we use $F_{rms} = 1 \cdot 10^{-7}$ (the global response remains identical below $F_{rms} = 1 \cdot 10^{-5}$). This deformation is expressed in terms of the shear strain $\gamma = \Delta x_x / L_y$, with Δx_x the relative displacement along the x-axis of the top of the simulation box with respect to the bottom of the box and L_y the distance between the top and bottom of the simulation box. The stress is obtained by calculating the virial stress based on the node positions $\mathbf{x} = [x_x, x_y, x_z]$, as follows: $\sigma_{kl} = \frac{1}{2V} \sum_{\langle ij \rangle} (x_k^{(j)} - x_l^{(j)}) f_l^{ij}$. Where k and l indicate the components of interest, e.g., for the shear stress we compute σ_{xy} . Furthermore, $V = L^3$ is the volume of the simulation box and f_l^{ij} is the l^{th} component of the force exerted on node j by node i . Please note that we report the reduced stress $\tilde{\sigma}_{kl} = \sigma_{kl} d^2 / \mu$.

To simulate plastic deformation by sliding of fibrils inside a fibre, we lengthen the bonds in the computational model by updating the rest length $l_{0,n+1} = l_{0,n} + l_{0,n} \lambda_p$ once the relative deformation $\frac{l - l_{0,n}}{l_{0,n}}$ exceeds the plasticity threshold λ_p , in both equations the subscript n indicates the number of lengthening steps such that $l_{0,0}$ is the initial rest length. The number of lengthening steps is not restricted (Extended Data Figure 8). The implementation of bond rupture, if the initial deformation threshold $\frac{l - l_{0,0}}{l_{0,0}}$ exceeds the rupture threshold λ_r , allows global fracture but does not affect the plastic regime as long as $\lambda_p \ll \lambda_r$ (Extended Data Figure 8). In the ideal case the plastic events are sequential, such that the implementation of the rupture algorithm cannot influence the fracture process. In other words, the applied deformation steps should be so small that only one segment exceeds a plasticity (and/or rupture) threshold after energy minimization. However, in decreasing the strain step there is trade-off with computation time. Therefore, we have implemented an adaptive strain step that is based on the closeness of bonds to the plasticity/rupture threshold, $\Delta\gamma = 1 - \Delta\lambda_{max}$ with a lower bound $\Delta\gamma_{min} = 5 \cdot 10^{-5}$ and verified that this does not affect the shape of the stress-strain response (Extended Data

Figure 8). In the event that multiple bonds exceed the threshold the bond that is stretched the most is lengthened/broken, followed by an energy minimization step, without updating the strain. This is repeated until no bond exceeds the plasticity/rupture thresholds.

In line with the experiments, we perform strain cycles on the networks. However, the strain is now varied over the range $[0, \gamma_{max}]$. After each cycle γ_{max} is increased with $\Delta\gamma_{max} = 0.25$.

Data and Materials availability

All relevant data and code used in the analysis relating to the modelling, shear rheology and optical tweezers are available in the following repository: DataverseNL. Methods and material for the synthesis of the monomer are previously reported²⁴. All additional methods and materials are available in the main text or supplementary information.

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Author contributions

VBV, JWS, FL, and TK designed the work. LCP and AK synthesised the monomers. FL, and JWS performed the bulk-rheology experiments. JT, SD and JvdG designed and performed the simulations, and JT performed data-analysis. VBV, LCP, and KMT designed, and VBV and LCP performed the optical tweezer experiment. MCAS, JWS and VBV performed the cryo-TEM experiments. VBV wrote the manuscript, with contributions by all the authors. All the authors commented on successive drafts and have given approval to the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper.

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