Shaping and structuring supramolecular gels

Phillip R. A. Chivers and David K. Smith

Department of Chemistry, University of York, Heslington, York, UK

Correspondence to D.K.S. david.smith@york.ac.uk

Abstract

Supramolecular gels assemble via non-covalent interactions between low-molecular-weight gelators (LMWGs). The gels form a solid-like nanoscale network spanning a liquid-like continuous phase, translating molecular-scale information into materials performance. However, gels based on LMWGs are often difficult to manipulate, easily destroyed and have poor rheological performance. The recurring image of newly-discovered supramolecular gels is that of an inverted vial showing that the gel can support its own weight against gravity. Such images reflect the limitation that these gels simply fill the vessel in which they are made, with limited ability to be shaped. This property prevents supramolecular gels from having the same impact as polymer gels, despite greater synthetic tunability, reversibility and bio/environmental compatibility. In this Review, we evaluate strategies for imposing different shapes onto supramolecular gels and for patterning structures within them. We review fabrication methods including moulding, self-healing, 3D printing, photopatterning, diffusion and surface-mediated patterning. We discuss gelator chemistries amenable to each method, highlighting how a multi-component approach can aid shaping and structuring. Supramolecular gels with defined shapes, or patterned structures with precisely-controlled compositions, have the potential to intervene in applications such as tissue engineering and nanoscale electronics, as well as opening-up new technologies.

Web summary

Supramolecular gels comprise low-molecular weight gelators that assemble by non-covalent interactions. In this Review, a range of fabrication methods, as well as strategies for shaping, structuring and patterning supramolecular gels are discussed.

[H1] Introduction

Low-molecular-weight gelators (LMWGs) self-assemble through non-covalent interactions into responsive and tuneable gel-phase materials.[1] The characteristics of these small-molecule gelators are translated up via hierarchical self-assembly into nanoscale fibres, and ultimately a macroscopic sample-spanning network (Fig. 1a).[2] The applications of supramolecular gels range from well-established technologies in lubrication, personal care, and the polymer industry, based on their rheological properties, through to proposed applications ranging from drug delivery and tissue engineering to nanoscale electronics and optical materials, based on the chemical information inherent within their structures.[3,4] However, the dynamic properties bestowed on these materials by non-covalent network linkages often come at the cost of mechanical strength. LMWGs thus tend to form weak gel networks compared with polymer gelators (PGs).[5]

The majority of supramolecular gels are formed as homogeneous materials in vials on treatment of a gelator solution with a stimulus (for example, heat, light, ultrasound or enzymes). Gelation is often initially evidenced by inverting the vial and observing a lack of flow under the force of gravity – such photographs are ubiquitous in the LMWG literature. However, to realise the full potential of LMWGs, we must fabricate gels with well-defined shapes and spatially-controlled structures (Fig. 1b, 1c). Gels with spatially-resolved structures and mechanical properties could, for example, direct stem cell fate for organ growth in vitro.[6] Shaped, degradable gels are also a focus for in vivo drug delivery and tissue engineering;[7] for example, implantable shaped gels can minimise abrasion-related inflammatory responses.[8] The precise structuring of conducting or resistive supramolecular gels may control electrical gradients and current flow across integrated soft electronic materials devices – systems that may ultimately interface with living systems.[9]

In this Review, we discuss strategies to shape and structure supramolecular gels. We assess the feasibility of different fabrication techniques and the advantages of shaping gels. We also show that multi-component gels can offer precise control[10] – however, such systems introduce complexity and must be effectively characterised to understand the interplay between components.[11] It is worth noting that many excellent examples from the extensive PG literature provide inspiration for spatially-resolved LMWG materials,[12,13,14] but here we focus on LMWG systems.

[H1] Moulding and self-healing

The simplest way of shaping gels is to mould and then release them in self-standing form, as is classically done in the kitchen when making jelly (jell-o). Surprisingly, however, there are relatively few studies where moulding has been reported for supramolecular gels. This may reflect researchers not attempting the experiment, but in our experience, only a limited range of supramolecular gels

have the rheological strength to be unmoulded and retain their shape. An early example is a sugar-based organogelator that formed self-standing objects at concentrations as low as 0.3% wt vol^{-1}.[15] It was argued that the high mechanical strength is likely a consequence of restricted conformational freedom and high intermolecular interaction affinity of the LMWG[16]. These gels were also formed in heavy oils like pump oil or silicone oil, rather than the more usual light organic solvents - this may have assisted the strength of the gel. Another robust gel based on an acid-amine salt in nitrobenzene as solvent could be moulded into a sculpture.[17] However, to create this moulded structure, a very high gelator loading (7% wt vol^{-1}) was required (Fig. 1d, left). A metallogel with similarly high loading (4% wt vol^{-1}) was moulded into a free-standing structure depicting a portrait of a girl.[18] In addition, robust free-standing gels ($G' \approx 300$ kPa) based on high loadings of a two-component gelator have been reported.[19] High loadings can also be used to create self-standing gels from a simple, industrially-relevant dibenzylidenesorbitol LMWG in deep eutectic solvents; these gels have high conductivity, and may have potential applications in energy technology.[20]

Most LMWGs assemble at <1% wt vol^{-1}, and many are insufficiently soluble to create networks at such high loadings. Nonetheless, for suitable LMWGs, high loading can help self-standing behaviour – for example, a series of gelators has reached yield stresses of 23 kPa at 5% wt vol^{-1}.[21] In these gelators, the maximum strength could be optimised by tuning the dual solvent, which also modified nanoscale morphology (Fig. 1d, middle). Optimising the balance between gelator solubility and insolubility can thus help develop stronger supramolecular gels with greater solid-like character. For example, optimising the amino acids on anthracenemethoxycarbonyl-capped dipeptides enabled the creation of self-supporting, moulded 3D hydrogels at lower loadings (~ 1% wt vol^{-1}).[22] These gels have antibacterial properties and are biocompatible towards human cells. Nonetheless, it is difficult to predict whether a gelator will be sufficiently robust to form self-standing gels. We suggest that a greater predictive understanding of the relationship between gelator chemical structure and mechanical performance, would be of extremely high value to researchers in the field. We believe it is likely that the impact of gelator structure on solubility and gel fibre stiffness will control this relationship.

Another strategy for enforcing shape onto LMWGs is to combine polymers with supramolecular gels (Fig. 1d, right).[10,23] In early work, the addition of small amounts of a soluble polymer to a LMWG converted an opaque viscous paste into a stable transparent gel.[24,25] It was argued that the polymer modified the nucleation growth mechanism of gel nanofibres, introducing crystallographic mismatch branching, modifying the gelation kinetics and leading to a more highly branched and interconnected network of fibres.[26,27] Recently, the addition of water-soluble poly(vinylalcohol) has been shown to increase the temporal and mechanical stability of a LMWG

hydrogel, which as a result, exhibited thixotropic behaviour.[28] However, polymer additives can also weaken supramolecular gels by changing the viscosity of the solution prior to gelation, impacting on self-assembly kinetics[29] and causing spherulitic nanoscale morphologies to become less interconnected and thus less capable of effective sample-spanning.[30] Clearly, optimisation of LMWG systems incorporating soluble polymers is required to maximise rheological outcomes.

Rather than formulating a soluble polymer into an LMWG, it is possible to create hybrid materials that incorporate a more robust polymer gel. This strategy is analogous with the formation of dual network polymer gels[31] and interpenetrated network polymer gels[32] which have been transformative in the field of polymer gel materials. The first example combining LMWGs with a PG used agarose to reinforce an LMWG and demonstrated that the mechanically reinforced hybrid gel could remove dyes from solution and re-release them.[33] When agarose was combined with a pH-responsive LMWG (DBS-CO_2H) based on 1,3;2,4-dibenzylidene-D-sorbitol (DBS), hybrid gels resulted that were physically robust (due to agarose), yet retained their pH-responsiveness (due to DBS-CO_2H).[34] The LMWG network could be assembled and disassembled within the hybrid gel by changing pH. The PG/LMWG approach has since been used to formulate self-standing gels in which an LMWG network based on DBS-$CONHNH_2$ remediates waste precious metals from the environment, reducing them to metal nanoparticles templated on the LMWG nanofibres.[35] The resulting gels containing Au nanoparticles were used as conductive materials for electrode modification, while those with Pd nanoparticles were used as environmentally-friendly reusable catalysts for Suzuki-Miyaura reactions.[36] This LMWG/PG approach has also been applied to develop heparin-release gels for drug delivery,[37] and tissue engineering materials in which the presence of the LMWG network ensured adhesion of the growing cells, even though the cells do not adhere to the agarose polymer gel alone.[38] In these cases, agarose acts as a robust inert PG matrix, allowing the LMWG to express its unique activity in readily-manipulated form. Similarly, hybrid guanosine/poly(*N,N*'-dimethacrylamide) gel networks maintain the luminescent LMWG properties but exhibit stretching ability and tear resistance as a consequence of the presence of the supporting polymer gel network.[39]

An advantage of supramolecular systems is their dynamic nature, which can enable gels to recover their materials performance after damage. This behaviour is termed thixotropic (a materials-level description) (Fig. 2). In the LMWG field, thixotropic gels are often referred to as self-healing.[40] In polymeric systems, self-healing requires that cleaved bonds within the polymer are re-formed (a molecular-level description).[41] Within the supramolecular polymers, which underpin self-assembled gels, the non-covalent interactions holding together the polymeric backbone are often reversible and thus have greater potential to be re-formed. However, to assign a material as self-healing requires careful characterisation that both rheological performance and underlying molecular self-assembled

structure have fully repaired. Rheologically, a gel has G' (storage modulus) > G" (loss modulus) by an order of magnitude – imposition of shear breaks down the gel such that G" > G' (Fig. 2b). For a self-healing system, removal of shear should then allow the gel to rapidly re-establish itself with G' and G" returning to their original values. This behaviour should be combined with a full repair of the underlying molecular and nanoscale structure. Such careful characterisation is not always the case in the literature, with some authors referring to any system which can reform into a gel as self-healing. This limitation should be noted.

If self-standing gels are cut into shapes, such as cubes, these shapes can act as building blocks to fabricate complex objects. In principle, supramolecular gel blocks may re-heal if the cut surfaces are joined together owing to their molecular-scale components, which can diffuse rapidly. However, not all LMWG systems self-heal due to their balanced solubility/insolubility,[42] meaning in many cases, gel nanofibres are non-dynamic, because they are effectively a precipitated form of the LMWG. In such cases, self-healing is challenging, because if the gel is broken down, the LMWG becomes insoluble under ambient conditions, and is thus unable to reassemble. This hypothesis is consistent with the fact supramolecular gelation usually requires a stimulus (for example, heat, ultrasound, solvent change and pH change) to encourage the system to dissolve and only subsequently self-assembles into solid-like nanofibres as it becomes less soluble again once the stimulus is removed.

Conceptually, self-healing has been exemplified by the creation of self-standing bridges by joining gel cubes, and healing between them (Fig. 1c). In an early report,[43] the gelator was a dendrimer reinforced with a nanoscale clay, relying on multivalent PG-like interactions to give the material strength. Since this report, this approach has been emulated by LMWG chemists. In one study, bridges could be built using a simple LMWG by fusing blocks of the gel (1% wt vol^{-1}) cut with a razor.[15] A pyrene-doped gel was fused to an undoped gel and pyrene slowly diffused across the interface, demonstrating exchange in the liquid-like phase across the self-healed area. More recently, the electrical conductivity of a dipeptide hydrogel was shown to recover on self-healing indicating that healed materials may be used to create shaped electronic devices with patterned conducting properties.[44] Self-healing studies were performed with other self-supporting gels.[17,18,21] When comparing PG and LMWG systems, it is noted that polymer gels are typically stronger but do not necessarily self-heal as quickly and can take hours or even days to self-heal compared with minutes for LWMG materials.[45] It was proposed that the greater molecular-scale mobility of LMWGs facilitates self-healing kinetics.

Many metallogels appear to demonstrate thixotropic properties. The binding of ligand to metal underpins formation of the metallogel gelators, and as such, the two components can be soluble, and only the complex need be insoluble to self-assemble. Therefore, we suggest that the gel

nanofibres can partly disassemble, retaining solubility and hence molecular-scale mobility. Similar arguments may be also applicable to other multi-component gels. A metallogel formed from the deprotonation of histidine in the presence of $Zn(NO_3)_2$ is thixotropic over at least three cycles, with rapid recovery of the gel on removal of strain.[46] Using this self-healing behaviour, four gel discs were joined together to form a self-standing column, which retained the rheological properties of the original gel. Similar properties have been demonstrated for mono-metallic and bi-metallic organogels.[47,48] Importantly, a self-healing metallogel based on copper acetate and oxalic acid (strictly, a coordination network gel, held together through metal-ligand bonds) is able to impart its self-healing performance to other non-healing gels (Fig. 2c).[49] For example, incorporating a 20% loading of this system into diaminocyclohexane-bis-amide gels, which cannot self-heal in their own right, induced self-healing. This addition of self-healing additives to non-healing gels enables repair and also shaping. Interestingly, two-component LMWGs have been used as supramolecular glue to enable polymeric hydrogels to be adhered to one another, demonstrating that not only can PGs enhance the robustness of LMWGs, but dynamic LMWGs can endow PGs with improved self-healing behaviour.[50]

Surprisingly, reports of more complex shapes formed via self-healing are limited.[51] Gel discs from a transparent self-healing gel formed on basification of dimethyl 2,6-pyridinedicarboxylate with KOH in methanol:water (9:1) were combined to yield self-standing columns, which were further stacked to form a gel gateway. These gels could be used as a fuel source, with the high methanol content making them flammable and the empty cells becoming reswollen in methanol to recharge.

These examples demonstrate that moulding and self-healing can create shaped gels that are more complex than the containers in which they form. If the gels have sufficient strength, or are reinforced with PGs, they can then be cut into any shape, which, if the gel is capable of self-healing, can be brought into contact to produce the required shape whilst retaining the original gel properties. By contacting gels with different compositions and healing interfaces, more complex patterned shaped gels may be possible. Individual components of these larger objects could be loaded with diffusionally-constrained species such as enzymes to spatially-define functionality, or the diffusion of small molecules through the gel could be used to create secondary networks within the self-healable gel.

[H1] 3D printing

3D printers are widely used to print polymers,[52] and polymer gels,[53] where rapid progress is being made with particular relevance to the fabrication of biomaterials and in bioprinting that incorporates cells.[54] The traditionally weak mechanical properties of LMWG-based gels, as well as the relatively

small number of gelators with appropriate thixotropic properties for extrusion have made progress comparatively slow. Nonetheless, 3D-printed LMWGs are beginning to emerge (Fig. 3). For example, a calixarene-based LMWG that formed thermally-initiated gels and importantly exhibited rapid thixotropy in organoalkoxysilanes was extruded from a hot solution in a syringe and reformed with shape control, enabling the creation of printed organogel shapes.[55]

In a key study, the 3D printing of dipeptide hydrogels using solvent and pH switching as gelation triggers was described (Fig. 3a).[56] To achieve high quality 3D printing, parameters such as extrusion volume and speed, printing height and printer movement speed were optimised. This approach printed complex, multilayer gels with defined positions and small dimensions (4 × 4 × 1 mm). The solvent switching method was more effective, which was thought to be a result of the spherulitic nanostructure that is much less perturbed by extrusion than the comparatively highly ordered extended fibrillar morphology formed by acidification. A significant number of LMWGs can be induced to form gels on solvent mixing or switching, and the generality of this approach could be widespread. It is likely that self-healing gels will become valuable for 3D printing. We also predict that multi-component gels, which form on mixing of two soluble components will be useful.

An alternative way of 3D-printing LMWGs is to combine them with polymers (Fig. 3b). In one example, a two-step enzyme-based 3D printing method[57] uses a naphthalene-tripeptide, functionalised with an acrylate, as the LMWG, which assembles on acidification. A mixture of glucose, horseradish peroxidase, acetylacetone and poly(ethylene glycol) methacrylate (PEGMA) is then added to this gel, followed by addition of glucose oxidase (GOx). GOx catalyses glucose oxidation, and the H_2O_2 formed as a by-product is converted into H_2O by horseradish peroxidase. The radical produced in this step is transferred onto acetylacetone, which initiates covalent polymerisation of the pendant acrylate on the LMWG network with PEGMA. Polymerisation increases the rheological properties of the gel by an order of magnitude, and because it is rapid, allows the LMWG precursor to be used as an ink and extruded to form multilayer shaped materials. By loading the precursor solution with fibroblasts, it was demonstrated that the process and resulting gel were highly biocompatible.

Interestingly, some patents explore a similar approach to develop phase change inks. For example, *trans*-1,2-cyclohexane bis(urea-urethane)s[58] which form gels as a result of intermolecular hydrogen bonding can incorporate polymerisable alkenes capable of photo-induced crosslinking. In addition, bis-urea gelators comprising photocurable monomers have been used in 3D printing technologies.[59] It was argued that combining supramolecular self-assembly with photo-induced polymerisation allowed stable raised print features to be rapidly built-up, without needing intermediate curing steps prior to photocuring of the final 3D printed object. This demonstrates the commercial potential of shaped LMWGs.

Recently, a number of other printable supramolecular gels have been reported. One printable example is a folate-based supramolecular hydrogel that assembles by π–π stacking and forms a gel on binding zinc(II) (the metal ion acts a crosslinking unit to create a 3D coordination polymer network, and hence this system is not strictly an LMWG).[60] This gel had robust mechanical properties even at concentrations below 1% wt vol^{-1}, and produced a variety of 3D structures by injecting the gel through syringes. Similarly, gels based on a G-quartet motif reversibly crosslinked with arylboronate units (albeit not strictly an LMWG, as it depends on reversible covalent bond formation for crosslinking), demonstrated thixotropic behaviour that was compatible with 3D printing through a bioprinter to generate 3D gel blocks of different shapes.[61] Demonstrating the value of this approach in high-tech applications, a gel based on G-quartet assembly crosslinked with boronic acid was used as an ink to print flexible electronic devices.[62] Moreover, the incorporation of hemin in these gels gave catalytically active materials and the in situ catalytic deposition of polyaniline on the nanofibres enabled the direct printing of a flexible electrochemical electrode. By loading this gel with glucose oxidase, a flexible glucose biosensor was developed.

Given the rapid developments in 3D printing, its use in LMWG chemistry is likely to grow rapidly. This will require chemical engineering expertise to be embedded in the organic chemistry labs that develop supramolecular gel systems. This technological transformation is underway and promises to offer rewards in a number of fields.[63,64] For example, 3D printing is compatible with biological cells, and hence could lead to the formation of shaped and structured LMWG materials for tissue engineering.[53]

[H1] Photopatterning

The most common method to induce spatial control over a material is to expose selected regions to electromagnetic radiation. This method has been prevalent with PGs, with numerous examples of light-controlled formation of shaped polymer gels for applications including tissue engineering,[65] and electronic devices.[66] Using supramolecular crosslinks enables the reversible shaping of polymer gels by light.[67] The formation and/or breakdown of a gel network can be controlled on the mesoscale by using photomasks, whilst on the microscale or nanoscale, one-photon and two-photon laser techniques can achieve precise spatial-resolution of these processes in 2D and 3D, respectively (Fig. 4).

The first example of a photo-patterned LMWG system was reported in 2004 and was based on a photo-degradable stilbene-based organogel.[68] The surfactant LMWG formed opaque organogels in toluene at high concentrations (8% wt vol^{-1}). On photo-irradiation, LMWG dimerisation leads to loss of gel behaviour, yielding a transparent sol. Performing photo-irradiation through a mask gave

some spatial control over the gel-sol transition leading to rudimentary patterning. It is likely that the high loading of the gelator helped provide macroscopic stability.

In 2005, reversible ring-closure of a dithienylcyclopentene derivative was used to spatially-control organogel assembly.[69] Both open and closed species assembled into sample-spanning networks in toluene, but under different conditions. At a concentration of 1.5 mM, conversion from the open to the closed form (initiated by UV light) resulted in a robust gel. This gel disassembled on exposure to visible light owing to ring opening, with the rate determined by intensity. Simultaneous and patterned exposure of a solution of the LMWG to UV and visible light created dynamic, reversible materials with microscale resolution and programmable lifetimes. These remarkable systems can be considered as write/read/erase gels.

Photo-responsive azobenzene chemistry can also achieve spatially-controlled sol-gel and gel-sol transitions.[70] Addition of water to a dimethylformamide solution of an azobenzene-functionalised benzene-1,3,5-tricarboxaminederivative resulted in gelation. Spatially-resolved gel breakdown was initiated by UV-triggered *trans-cis* isomerisation of the peripheral azobenzenes, disrupting intermolecular hydrogen bonding (Fig. 4b, top). Rapid regeneration of the *trans*-azobenzene by exposure to visible light resulted in recovery of the gel and erasure of the pattern. This write/read/erase cycle took <4 min, in contrast to longer timescales required for the system described above (>1 h).[69] It was argued that the short cycle time is more practical for supramolecular memory systems.

In 2008, light-responsive hydrogels based on a glycolipid LMWG with a fumaric amide linker were reported (Fig. 4b, bottom).[71] Exposure to UV light resulted in *trans-cis* isomerisation, converting the fumaric amide into the maleic amide, with the loss of hydrogen-bond interactions causing a gel-sol transition. A focussed laser spatially controlled gel breakdown and photolithography created sol 'spots' within the gel. These materials achieved spatiotemporal control over the diffusion of biomacromolecules. In later work, laser beams created channels through these gels, which were seeded with cells.[72] Two cell types were cultured in the channels – demonstrating the potential for tissue engineering.

In 2012, photo-acid induced transitions were shown to spatially-resolve assembly. More specifically, a photo-acid generator protonates the carboxylic acid of a naphthalene dipeptide hydrogelator (Fig. 4c, top).[73] Diphenyliodonium nitrate (DPIN) was the photo-acid generator, with UV irradiation converting the photo-acid generator into iodobenzene, phenol and nitric acid, lowering the

pH and hence switching on gelation. By using a mask, only the region of the sample exposed to the UV-light was acidified and hence converted into a gel. For such systems, it is important that gelation kinetics are faster than molecular-scale diffusion and convection, as these processes limit resolution.

In 2015, an alternative photo-acid generator was reported to initiate gel formation (Fig. 4c, bottom).[74] Merocyanine cyclises on exposure to visible light to form a spiropyran, liberating a proton. Crucially, when irradiation ceases, the spiropyran rapidly reverts to the merocyanine, ensuring acidification is confined to areas exposed to light. By incorporating this photo-acid generator into a mixture of aldehyde and tris-acyl hydrazide, acid-catalysed formation of a tris-hydrazone gelator and subsequent self-assembly was achieved in a spatially-controlled manner using a laser-printed photomask. The rate of gelation was slow compared to catalyst deactivation in the shielded regions, and therefore, microscale resolution was possible, with diverse shapes being patterned.

Later studies used the same photo-acid generator to elicit the opposite response from an amine-terminated diphenylalanine organogel.[75] On UV-exposure, the terminal amine was protonated, causing gel breakdown owing to an increase in electrostatic repulsion between gelators. This process was reversed on removal of the stimulus, allowing spontaneous reformation of the gel on a relatively short timescale (< 20 min). Self-erasing patterns were made in a bulk gel using a photomask, with UV-exposed regions undergoing three reversible gel-sol transitions without loss of resolution.

An elegant approach to photo-triggered gelation involves disruption of gelator-gelator interactions by clipping a photo-degradable macrocycle around a perylene bisimide (PBI) gelator.[76] The macrocycle prevents formation of hydrogen bonds between PBI units until UV light is applied. Photolytic cleavage of the macrocycle reveals the hydrogen bonding moieties, causing gelation. Interestingly, solvent has a crucial role in controlling the resolution. In organic solvents, rapid gelation kinetics prevent diffusion of free PBI and confine assembly to stimulated areas, but in aqueous media, the greater solubility of PBI slows gelation, resulting in lower resolution.

Recently, a 6-nitroveratryloxycarbonyl-protected dipeptide hydrogel for the light-controlled release of therapeutic agents (for example, insulin) was reported.[77] Unlike the more common fluorenylmethyloxycarbonyl (Fmoc)-protected peptide gels, these materials undergo UV-triggered disassembly via photo-induced, irreversible cleavage of the protecting group, with the resulting loss of π-π stacking interactions inducing rapid gel disassembly and insulin release in exposed regions. It was suggested that two-photon near-IR irradiation could spatially control gel breakdown and release in vivo.

In addition to using light to pattern gels, it can give some nanoscale morphological control. For example, in photo-switchable dithienylethene-tripeptide hydrogelators,[78] the dithienyl group undergoes partial cyclisation (open/closed ratio = 52:48) on UV irradiation, followed by ring-opening in response to visible light (open/closed ratio = 92:8). Differences were visualised by transmission electron microscopy in the aggregate morphologies of irradiated and non-irradiated samples. These morphological changes were not manifested in a change in rheological performance, but emission properties were altered, allowing a readable and rewritable pattern to be etched into the gel.

Recent work achieved spatially-resolved morphological control[79] in gels formed by reaction of a hydrazine-functionalised calixarene with an aldehyde-bearing stilbene derivative. The resulting gels had blue fluorescence, attributed to H-aggregate assembly. Under UV light, the stilbene moieties underwent [2+2] cycloaddition resulting in a loss of fluorescence. This process covalently links the gel nanofibres and enhances mechanical robustness by three orders of magnitude. In contrast, J-aggregates do not undergo [2+2] cycloaddition. By combining thermal pre-treatment of the gel (converting some of the H-aggregates into J-aggregates) with controlled UV-exposure, spatially-resolved control over gel composition was achieved.

Reversible photoreduction of a valine-appended perylene bis-imide gelator has been used to give control over gel mechanical properties.[80] Bulk gelation was achieved through hydrolysis of glucono-delta-lactone (GdL), which lowers pH in a controlled manner. Exposure of the sample to UV light (λ = 365 nm) then initiated formation of a radical anion of the perylene unit, increasing the mechanical strength of the gel for 24 h (the lifetime of the radical anion). Small angle neutron scattering revealed that irradiating the sample increases the density of fibres, and DFT calculations predicted this increase is a result of contraction of the inter-gelator and inter-fibre distances through anion-π interactions. Dynamic nanoindentation confirmed that the application of UV light only to certain areas, restricted mechanical change to these regions. This work demonstrates that photo-patterning can impact macroscopic gel properties in a spatially-resolved way as a result of localised modifications to nanoscale morphology – an example of gel structuring.

To gain additional functionality in spatially resolved photo-controlled gels, LMWGs have been combined with liquid crystal phases. The presence of the liquid crystal can enforce morphological constraints on the gel network.[81,82] For example, the photo-induced *trans*-*cis* isomerisation of an azobenzene-containing LMWG induced gel breakdown, accompanied by cholesteric liquid crystal-phase formation in the irradiated areas. Subsequent conversion back to the gel-forming *trans*-isomer resulted in gel reformation, the microstructure of which was then templated by the liquid crystal phase, giving rise to alignment of the gel nanofibres in these domains. This synergistic approach to the

control of the liquid crystal phase behaviour and the gel morphology is reversible – the application of heat erases the pattern, which can be reformed by repeating the procedure.

There is increasing interest in photo-patterning multi-component gel systems (Fig. 5). These approaches offers advantages – for example, a pre-formed supporting gel network can limit convection and diffusion, enforcing better spatial resolution as a second gel network gets patterned-in. Multiple components also introduce the possibility of orthogonal functionalities in a spatially-resolved manner to achieve multi-functional applications.

In 2014, patternable hybrid LMWG/PG hydrogels were reported.[83] A 1,3:2,4-dibenzylidenesorbitol-based LMWG (DBS-CO_2H) was combined with a poly(ethylene glycol) dimethacrylate (PEGDM) monomer (Fig. 5b). Crosslinking PEGDM via exposure to UV light generated the PG, while the DBS-CO_2H hydrogelator (pK_a, 5.4) self-assembled via slow acidification with GdL. All components were mixed together, and UV irradiation was performed using a photomask to achieve spatial resolution of the PG. The regions of the gel exposed to UV light were more robust, allowing these hybrid PG/LMWG domains to be removed intact from the much softer bulk LMWG – in this way, the photo-patterned PG enforces a self-standing shape onto the LMWG. The LMWG retained its properties within the PG, being assembled/disassembled within the shaped hybrid gel on changing pH.

In subsequent research, the LMWG was modified from DBS-CO_2H to DBS-$CONHNH_2$,[84] which is thermally triggered (Fig. 5b). In this case, the self-assembled LMWG was assembled first, and the PEGDM PG network was subsequently patterned-in. This method has advantages in terms of spatial control, as the pre-formed LMWG network limits convection and diffusion. The resulting gels were self-standing, with the polymer gel imposing shape onto the LMWG. Importantly, DBS-$CONHNH_2$ retained its unique properties, interacting reversibly with acidic compounds, such as non-steroidal anti-inflammatory drugs and releasing them in a pH-dependent manner. Indeed, a shaped hybrid gel selectively released naproxen in a directional manner, mostly into solution-phase compartments of elevated pH.

In addition to using a PG to pattern a LMWG, one LMWG network can be patterned within another – a process called positive writing. Positive writing has been achieved using two acid-triggered gelators with different pK_a values (DBS-CO_2H, ca. 5.4 and DBS-Gly, ca. 4.3) (Fig. 5c).[85] A mixture of the two gelators was activated using two proton sources (GdL and DPIN). Just enough GdL was added to assemble DBS-CO_2H, and as the supply becomes exhausted, subsequent photo-irradiation reduces pH further through DPIN activation, resulting in the assembly of the second DBS-Gly network in the first network. NMR spectroscopic studies demonstrated the largely orthogonal assembly of these two LMWGs. Photo-irradiation under a mask gave patterned materials, with

excellent resolution. The formation of the second network yielded gel domains with different network compositions and significant pH differences, maintained for a period of days, as visualised using indicator dyes. In principle, these patterned gels can be erased (disassembled) by adding base, and then rewritten by sequential acidification.

In contrast to the positive writing approach, a negative-writing approach can be used, in which one network within a multicomponent gel is broken down (Fig. 5c).[86] Stepwise acidification using a single proton source (GdL) triggered self-sorted stepwise gelation of a carboxylic acid-functionalised *trans*-stilbene gelator (pK_a *ca*. 5.8) and dipeptide gelator (pK_a *ca*. 5.0), with both LMWGs assembling throughout the material. Subsequent irradiation using a 365 nm LED caused *trans-cis* isomerisation of the stilbene, selectively disassembling the corresponding network. ^{1}H NMR spectroscopy confirmed this was confined to regions where light penetrated the sample. This generated a gel with different domains containing either single or dual networks, the same end-point achieved using positive writing, but applying stimuli in a different order.

An example of a photopatterned multicomponent gel, reported in 2017, is based on dual-network organogels comprising self-sorted anthracenylacylhydrazone and a fluorescent hydrazide derivative.[87] Once again, one of the networks (the acylhydrazone) was selectively removed through photo-isomerisation. In this case, however, the network did not break down as a direct consequence of visible light exposure. Disassembly only occurred when light emitted by the other fluorescent (hydrazide) network was absorbed, inducing *trans-cis* isomerisation. The presence of one network is thus essential to trigger the breakdown of the other; that is, co-operative disassembly. The mechanical properties and wettability of irradiated regions, were similar to those of the single component gel. Spatial resolution could also be visualised, as disassembly of the anthracenyl J-aggregates resulted in much weaker emission under UV light than in regions where both networks remained intact

Gel photopatterning is a simple approach to achieve spatial resolution and we anticipate it will continue to be exploited, possibly alongside other shaping approaches to yield more sophisticated materials. In the future, positive and negative writing approaches may be combined to generate more complex patterned multi-component gels. It is also important to note that in self-assembled gels the history of the material plays a role in controlling its properties. Control over kinetic gel-assembly pathways and metastable states will be increasingly important in maximising the potential of supramolecular materials.[88,89] Furthermore, at present , photoirradiation often only achieves 2D pattering by using masks and we suggest that 3D photo-patterning using two-photon methods, will become more prevalent.

[H1] Diffusion control

In hierarchical LMWG self-assembly, the rate of transport of gelator to the site of fibre growth has profound impact on the kinetics of network formation and resulting materials properties.[90] However**,** diffusion processes have also been used to fabricate gels with spatio-temporal control (Fig. 6).

Seminal work used agar or preferably alginate polymer gels as a matrix to control the diffusion of reagents and hence template the reaction between a tris-hydrazide and three equivalents of aldehyde, leading to a tris-hydrazone which subsequently self-assembles (Fig. 6).[91] Reservoirs were cut in the alginate gel matrix to separate the reactive components at the start of the experiment. The gelator precursors then diffuse through the alginate gel – when the precursors come into contact they react and spontaneously assemble into an opaque gel. The final shapes are determined by the shapes of the reservoirs and their relative locations (Fig. 6b). Dissolving the calcium alginate gel with ethylenediaminetetraacetic acid (EDTA) yielded self-standing tris-hydrazone hydrogel structures, multiple millimetres in size. Once again, this approach demonstrates how a pre-existing PG network can provide robustness and prevent convection. Fascinatingly, spatial control of chemical functionality was achieved by loading different reservoirs with different aldehydes. The composition of gels formed at each location depended on which aldehydes were present there as a result of diffusion.

Spatially-resolved gel formation on the micrometre scale was also achieved using a wet-stamping method.[91] A shaped agar stamp containing a pre-gelator component was placed in contact with an alginate substrate into which the complementary reactive component was formulated. At the interface, diffusional exchange of reactive components occurred and spontaneous network formation was observed. The alginate substrate could be removed using EDTA to yield hydrazone hydrogels at resolutions of 200 μm.

Diffusion across a gel-gel interface has been explored using a dynamic two-component organogel (comprising an acid and an amine) (Fig. 6c).[92] Each component can de-complex from the other and diffuse through the gel; indeed, the two components can be considered as pre-gelators. When two gels with different compositions were placed in contact with one another, the individual pre-gelator components could exchange between them, leading to changes in gel composition on each side of the interface, and impacting on the nanoscale morphology in these regions. For example, two different amines could exchange with one another across the interface, changing the composition of the gel, especially around the interface. Alternatively two different acids, with opposite chiralities, could exchange with one another. This study demonstrated a surprising degree of dynamic character,

even in the supposedly solid-like nanofibres of these supramolecular gels. These gels combine reaction diffusion and self-healing concepts to yield materials that develop gradient-like concentration profiles around a gel-gel interface, however, in this case, the resulting gels were not self-standing. Nonetheless, this report demonstrates a unique way in which patterning can be imposed within a single block of gel via diffusion processes.

Indicating how diffusion and spatial control can lead to unique functionality, urease enzymes have been trapped in specific locations in calcium alginate polymer gels. Diffusing urea through the gels then undergoes spatio-temporally controlled processes, which can induce colour changes, or localised gel disassembly.[93] There is much to learn conceptually from this research that could be useful to supramolecular chemists. However, as yet, LMWGs have not been included in these systems.

Control of reaction-diffusion processes is a powerful way of controlling gel assembly/disassembly in defined locations. The principles outlined here could, with programmable lifetimes and release profiles, ultimately find applications in microfluidics, or in sophisticated sensing or delivery devices for use in vivo. The formation of spatially-resolved gels by controlled diffusion may also be achievable in formal microfluidic experimental set-ups, and such systems are discussed further in the following section.

[H1] Surface-mediated patterning

Gels can be shaped and patterned by triggering a surface-mediated event.[94,95] For example, electrochemical methods can control self-assembly of gels on a surface (Fig. 7).[96] The oxidation of hydroquinone was driven electrochemically, liberating two protons at the working electrode, with the rate of acidification close to the working electrode being determined by the applied current (Fig. 7a). On acidification to a pH below the pK_a of a dipeptide LMWG, gelation was initiated on the electrode, with gel thickness determined by applied current and time (Fig. 7b). Complex spatial and temporal control of dipeptide gel formation could be achieved by controlling the location and time at which the current is applied. For example, by shielding regions of fluorine-doped tin oxide using insulating masks, gels with cavities were formed. These cavities could subsequently be filled with a different gelator solution and current re-applied, forming spatially-patterned gels with distinct chemical and rheological properties. By applying different currents, a gel with varying and controllable thicknesses could be formed. Additionally, multi-layer and multicomponent gels were created by modifying the LMWG to which the electrodes were exposed at a given time. This is therefore a versatile approach to gel structuring, although the presence of the electrode substrate probably helps mechanically

reinforce the gels formed. Other ways of strengthening the resulting objects, such as incorporating PGs, can easily be visualised.

It was demonstrated that a hydrogel-coated nanoelectrode array created on a surface using methods such as those described above could act as a biosensor.[97] Once again, the gel varied in size and thickness from nanoscale, to microscale and macroscale, depending on the area exposed to the current and the magnitude of the current, respectively.The hydrogel mesh varied in density, which was greater close to the electrode. The hydrogel structure could be firmly anchored to and through an established clinically relevant biosensing layer without compromising detection, and was capable of preventing protein biofouling whilst enabling smaller molecules to pass through the hydrogel matrix and be detected.

Redox-switchable metallogels are prevalent in the literature,[98] yet surprisingly, attempts to use eletrochemical techniques to control and pattern gelation are very rare. It can be envisaged that spatially-resolved electrochemically-controlled metal redox processes could, in the future, generate dynamic, reversible and functional spatially-resolved metallogels.

Alternatively to electrochemical approaches, patterned surfaces can catalyse gel formation in a localised manner (Fig. 8). This was achieved using a tris-hydrazone gelator with gelation being localised to pre-defined areas of a glass slide by micro-patterning catalytic sulfonic acids onto a hydroxysilane-functionalised glass slide using soft lithography (Fig. 8b).[99] On contact with a solution of aldehyde and tris-hydrazide, assembly only occurred on regions of the surface where the acid catalyst was. The maximum height of the gel micropatterns was only 5.5 μm, which may result from the catalytic sites becoming shielded from the reactants as gel assembly progresses. Micropatterned materials are of interest for fundamental research into the response of cells to mechanical stimuli and biosensors, while bulk patterning may be of use in reactor design.

A similar approach has been employed for the enzyme-mediated spatially-controlled production of gel-forming Fmoc-peptides (Fig. 8c).[100] An endoprotease (thermolysin) was covalently localised on an amino-functionalised PEG surface. On exposing the surface to a solution of Fmoc-phenylalanine and phenylalanine derivatives, peptide coupling to form a Phe-Phe dipeptide, followed by self-assembly was only observed in the enzyme-functionalised regions. Gel formation was confirmed by Congo Red staining, demonstrating the spatial-resolution. Controlled nucleation of gel fibres around thermolysin, which can catalyse the peptide bond formation, was necessary for gelation. When the protease chymotrypsin was immobilised onto surfaces, no gelation was observed, confirming self-assembly was the result of an enzyme-mediated reaction, rather than a non-specific aggregation event associated with surface patterning. In subsequent work, it was demonstrated that

the same enzyme could be encapsulated in a polydopamine layer.[101] Through careful control of washing procedures, the relative quantities of irreversibly and reversibly encapsulated enzyme were modified, with the ratio of the two controlling gel height.

Given the large number of enzyme-triggered peptide gels,[102] this approach to surface patterning could be used to develop wide-ranging systems with spatial control over the assembly (or disassembly) of different peptide nanofibres. For example, by spatially-defining a second enzyme on the surface, controlled formation of two different gel networks could be promoted to form a spatially-resolved multicomponent gel with surface-mediated control over chemical and structural properties.

Combining concepts of electrochemistry and enzyme-mediated patterning, an electrochemical system was developed in which immobilised glucose oxidase on the surface gave rise, in the presence of oxygen, to a flow of protons as a result of glucose oxidation.[103] The confined acidic environment at the solid-liquid interface enabled the protonation of a dipeptide LMWG, from and close to the surface, leading to self-assembly. Depending on the period of contact between the dipeptide and the surface, the deposited thickness varied from 1-5 μm.

In a recent report, a simple approach to surface-assisted self-assembly using proton diffusion from a poly(dimethyl)siloxane cube pre-soaked in HCl has been outlined.[104] An acid-sensitive LMWG self assembled on the cube surface, with the gel front increasing by ~ 3 μm s^{-1}. It was important to tune the nature of the surface – diffusion must be slower than the nucleation rate (this was not the case, for example, when using agarose cubes). A microfluidic device was also used to control proton diffusion – indeed, the self-assembly of gels in microfluidic devices is an emerging field,[105,106] and may offer fascinating ways of achieving spatially constrained assembly.[107]

A combination of surface-mediated processes with concepts of self-healing was reported to give unique shaped hydrogels.[108] A drop of peptide amphiphile LMWG solution was added to an elastin-like protein (ELP), causing the assembly of a nanofibrous membrane separating the two solutions as a consequence of interactions between the hydrophobic binding domains of each. Intriguingly, the assembled membrane adhered to the closest surface in its container and then opened up to form a 3D hollow gel tube, maintaining separation of the ELP and LMWG solutions. Contacting the tube with additional surfaces led to anisotropic extension, to generate complex self-healable structures, which could be removed from solution and handled. These tubular structures controlled the growth of mouse adipose-derived stem cells and human umbilical vein endothelial cells. This system has since been further modified to make microfluidic devices that control gel membrane formation kinetics and thickness by modulating the individual component flow rates.[109] Using 3D printing, fine control could be achieved to generate shaped sequences of hollow cylindrical gel membranes, whilst substitution of the ELP for a solution of keratin resulted in alignment of LMWG

nanofibres.[110] This work demonstrates how combining a variety of fabrication techniques with carefully-chosen chemistries can yield highly complex and responsive, shaped and patterned gels.

[H1] Outlook

The precise shaping and patterning of LMWG-containing gels will increase the complexity of supramolecular gels, and hence enable more sophisticated outcomes than the rheological uses they have already found in industry. Although LMWG fabrication is at an early stage, the use of new techniques to generate functional gels could open up increasingly advanced applications to these simple, readily-accessible molecular materials. For example, robust gels that can be shaped into the desired form, and patterned with conducting pathways and resistive areas may be of high value in nanoscale electronics. In tissue engineering, precise spatial and temporal control of gels to yield patterned materials, can inform interactions with growing tissue. New technologies may also emerge, such as microfluidic gels and innovative flow systems, or soft nanoscale devices implanted in vivo.

In the simplest terms, gels can be moulded into self-standing objects, but many self-assembled gels are too weak. Controlling gelator loading or solubility can enhance rheological performance and hybrid LMWG/PG approaches can endow LMW gels with greater stability while retaining their function. Self-healing is a key mechanism to fuse together LMW gels to generate more complex, multi-functional architectures. The discovery of self-healing, stimulus-free LMWGs, particularly those that impart their properties onto other materials, is highly desirable, with multi-component gels having particular promise.

3D printing has significant potential for gel shaping, and we suggest it will be of particular value when combined with hybrid multi-component systems and photo-patterning. The application of 3D printing with LMWGs is at an early stage, and the optimisation of parameters and materials for this approach is just beginning. We suggest that adapting this low-cost methodology will make it a routine way of fabricating complex, multi-component gels, in which different domains have different compositions, and may offer a simple route to the large-scale fabrication of devices incorporating LMWGs.

Spatially-resolved application of stimulus can control LMWG assembly. Photopatterning is dominant in initiating the assembly, breakdown or morphological change of gels. In isomerisation-mediated photopatterning, these changes are often reversible, allowing patterns to be written and erased. Photoacid generators allow gelators that are not inherently UV-active to be patterned by light and can be erased using a base. Assembly kinetics must be faster than diffusion and convection, and the use of a background gel to support patterning can be valuable. Given the prevalence of photopatterning in materials fabrication, it seems likely that its use with LMWGs will increase.

Reaction diffusion makes use of the inherent porosity of gels and their compatibility with chemical reactions, and can generate complex, dynamic materials with inherent structural and chemical gradients. This approach may enable the fabrication of devices with temporal as well as spatial resolution, which is useful for tissue engineering, where evolution of the gel over time, or in response to different stimuli associated with cell growth, is desirable.

Patterning catalytic sites onto a surface provides an alternative method for precisely-defined LMWG assembly. An electrochemical stimulus can also be an effective way to trigger assembly. The control of diffusion and assembly rates is essential in such systems, which can be used to assemble gelators at pre-defined locations with controlled thicknesses. Soft-solid modified surfaces have, in particular, wide-ranging potential uses in electronic devices and microfluidics. We also note that microfluidics itself offers an intriguing approach for controlling LMWG assembly processes.

The range of available fabrication methods will, over time, increase the complexity of supramolecular gels, particularly enabling the incorporation of multiple active components. The use of different gelators that can be shaped using orthogonal methods should allow further sophistication to be programmed into LMWG-containing materials, creating shaped self-standing gels with chemical and structural heterogeneity in 3D. We also anticipate significantly more interest in the temporal properties of these materials, in particular their ability to adapt and evolve.

In the future, it is therefore likely that studies of supramolecular gels will report not only the discovery of new gelation motifs and develop an understanding of structure-activity relationships, but will crucially explore and optimise the fabrication techniques that can allow these materials to be controlled, shaped and patterned. We anticipate that design rules and threshold parameters will emerge that will constitute the requirements for a supramolecular gel to be shaped and structured in specific ways. Taking this approach will allow these materials to be harnessed for a wider range of applications, breaking-through the limitations of the inverted vial. Clearly, this step-change in the field of supramolecular gels necessitates a fusion of skills between chemistry and chemical engineering. Precise chemical structural optimisation will be required to enable different fabrication engineering techniques, and in this way, the inherent molecular nature of these materials will continue to lie at the heart of their behaviour. With such technologies in hand, the supramolecular gel chemist will be able to develop these highly-tunable and fascinating soft materials, and proceed to tackle truly interdisciplinary problems.

[H1] References

1 Weiss, R. G. The Past, Present, and Future of Molecular Gels, What is the Status of the Field, and Where is it Going? *J. Am. Chem. Soc.*, **136**, 7519-7530 (2014).

2 Draper, E. R. & Adams, D. J. Low-Molecular-Weight Gels: The State-of-the-Art. *Chem*, **3**, 390-410 (2017).

3 Smith, D. K. in *Molecular Gels: Structure and Dynamics*, (ed. Weiss, R. G.) 300-371 (Royal Society of Chemistry, Cambridge, 2018).

4 Okesola, B. O., Vieira, V. M. P., Cornwell, D. J., Whitelaw, N. K. & Smith, D. K. 1,3:2,4-Dibenzylidene-D-sorbitol (DBS) and its Derivatives – Efficient, Versatile and Industrially-Relevant Low-molecular-weight Gelators with over 100 Years of History and a Bright Future, *Soft Matter*, **11**, 4768-4787 (2015).

5 Bohidar, H. B., Dubin, P. & Osada, Y. (eds.) *Polymer Gels: Fundamentals and Applications*, (American Chemical Society, Washington DC, 2002).

6 Slaughter, B. V., Khurshid, S. S., Fisher, O. Z., Khademhosseini, A. & Peppas, N. A. Hydrogels in Regenerative Medicine *Adv. Mater.*, **21**, 3307-3329 (2009).

7 Skilling, K. J., Citossi, F., Bradshaw, T. D. Ashford, M., Kellam, B. & Marlow, M. Insights into Low Molecular Mass Organic Gelators: A Focus on Drug Delivery and Tissue Engineering Applications. *Soft Matter*, **10**, 237-256 (2014).

8 Li, J. & Mooney, D. J. Designing Hydrogels for Controlled Drug Delivery. *Nature Rev. Mater.*, **1**, 16071 (2016).

9 Zhang, A. & Lieber, C. M. Nano-Bioelectronics. *Chem. Rev.*, **116**, 215-257 (2016).

10 Buerkle L. E. & Rowan, S. J. Supramolecular Gels Formed from Multi-Component Low Molecular Weight Species. *Chem. Soc. Rev.*, **41**, 6089-6102, (2012).

11 Draper, E. R. & Adams, D. J. How Should Multicomponent Supramolecular Gels be Characterised? *Chem. Soc. Rev.*, **47**, 3395-3405 (2018).

12 Khademhosseini, A., Langer, R., Borenstein, J., Vacanti, J. P., Microscale Technologies for Tissue Engineering and Biology. *Proc. Natl. Acad. Sci. USA*, **103**, 2480-2487 (2006).

13 Leijten, J., Seo, J., Yu, K., Trujillo-de Santiago, G., Tamayol, A., Ruiz-Esparza, G. U., Shin, S. R., Sharifi, R., Noshadi, I., Alvarez, M. M., Zhang, Y. S., Khademhosseini, A. Spatially and Temporally Controlled Hydrogels for Tissue Engineering. *Mater. Sci. Eng. R*, **119**, 1-35 (2017).

14 Suntornnond, R., An, J., Chua, C. K. Bioprinting of Thermoresponsive Hydrogels for Next Generation Tissue Engineering: A Review. *Macromol. Mater. Eng.* **302**, 1600266 (2017).

15 Vidyasagar, A., Handore, K. & Sureshan, K. M. Soft Optical Devices from Self-Healing Gels formed by Oil and Sugar-Based Organogelators. *Angew. Chem. Int. Ed.*, **50**, 8021-8024 (2011).

16 John, G., Jadhav, S. R., Menon, V. M. & John, V. T. Flexible Optics: Recent Developments in Molecular Gels. *Angew. Chem. Int. Ed.*, **51**, 1760-1762 (2012).

17 Sahoo, P., Sankolli, R., Lee, H.-Y., Raghavan, S. R. & Dastidar, P. Gel Sculpture: Moldable Load-Bearing and Self-Healing Non-Polymeric Supramolecular Gel Derived from a Simple Organic Salt. *Chem. Eur. J.*, **18**, 8057-8063 (2012).

18 Yan, L., Gou, S., Ye, Z., Zhang, S. & Ma, L. Self-Healing and Moldable Material with the Deformation Recovery Ability from Self-Assembled Supramolecular Metallogels. *Chem. Commun.*, **50** 12847-12850 (2014).

19 Park, J., Kim, K. Y., Kim, C., Lee, J. H., Kim, J. H., Lee, S. S., Choi, Y. & Jung J. H. A. Crown-Ether-Based Moldable Supramolecular Gel with Unusual Mechanical Properties and Controllable Electrical Conductivity Prepared by Cation-Mediated Cross-Linking. *Polym. Chem.*, **9**, 3900-3907 (2018).

20 Ruiz-Olles, J., Slavik, P. & Smith, D. K. Self-Assembled Gels Formed in Deep Eutectic Solvents: Supramolecular Eutectogels with High Ionic Conductivity. *Angew. Chem. Int. Ed.*, **58**, 4173-4178 (2019).

21 Xu, Z., Peng, J., Yan, N., Yu, H., Zhang, S., Liu, K. & Fang, Y. Simple Design but Marvelous Performances: Molecular Gels of Superior Strength and Self-Healing Properties. *Soft Matter*, **9**, 1091-1099 (2013).

22 Gavel, P. K., Dev, D., Parmar, H. S., Bhasin, S. & Das, A. K. Investigations of Peptide-Based Biocompatible Injectable Shape-Memory Hydrogels: Differential Biological Effects on Bacterial and Human Blood Cells. *ACS Appl. Mater. Interfaces*, **10**, 10729-10740 (2018).

23 Cornwell, D. J. & Smith, D. K. Expanding the Scope of Gels – Combining Polymers with Low-Molecular-Weight Gelators to Yield Modified Self-Assembling Smart Materials with High-Tech Applications, *Mater. Horiz.*, **2**, 279-293 (2015).

24 Liu, X.-Y. & Sawant, P. D. Micro/Nanoengineering of the Self-Organized Three-Dimensional Fibrous Structure of Functional Materials, *Angew. Chem. Int. Ed.*, **41**, 3641-3645 (2002).

25 Liu, X.-Y., Sawant, P. D., Tan, W. B., Noor, I. B. M., Pramesti, C. & Chen, B. H. Creating New Supramolecular Materials by Architecture of Three-Dimensional Nanocrystal Fiber Networks, *J. Am. Chem. Soc.*, **124**, 15055–15063 (2002).

26 Li, J.-L. & Liu, X.-Y. Microengineering of Soft Functional Materials by Controlling the Fiber Network Formation, *J. Phys. Chem. B*, **113**, 15467–15472 (2009).

27 Li, J.-L., Yuan, B., Liu, X.-Y., Wang, X.-G. & Wang, R.-Y. Kinetically Controlled Homogenization and Transformation of Crystalline Fiber Networks in Supramolecular Materials, *Cryst. Growth Des.*, **11**, 3227–3234 (2011).

28 Mahapatra, R. D., Dey, J. & Weiss, R. G. Poly(vinyl alcohol)-induced Thixotropy of an L-Carnosine-based Cytocompatible, Tripeptidic Hydrogel, *Soft Matter*, **15**, 433-441 (2019).

29 Chen, L., Revel, S., Morris, K., Spiller, D. G., Serpell, L. C. & Adams, D. J. Low Molecular Weight Gelator-Dextran Composites *Chem. Commun.*, **46**, 6738–6740 (2010).

30 Pont, G., Chen, L., Spiller, D. G. & Adams, D. J. The Effect of Polymer Additives on the Rheological Properties of Dipeptide Hydrogels, *Soft Matter*, **8**, 7797–7802 (2012).

31 Gong, J. P, Why are Double Network Hydrogels so Tough? *Soft Matter* **6**, 2583-2590 (2010)

32 Dragan, E. S. Design and Applications of Interpenetrating Polymer Network Hydrogels. A Review. *Chem. Eng. J.* **243**, 572-590 (2014).

33 Wang, J. Wang, Z., Gao, J., Wang, L., Yang, Z., Kong, D. & Yang, Z. Incorporation of Supramolecular Hydrogels into Agarose Hydrogels – A Potential Drug Delivery Carrier. *J. Mater. Chem.*, **19**, 7892-7896 (2009).

34 Cornwell, D. J., Okesola, B. O. & Smith, D. K. Hybrid Polymer and Low-Molecular-Weight Gels – Dynamic Two-Component Soft Materials with Both Responsive and Robust Nanoscale Networks. *Soft Matter*, **9**, 8730-8736 (2013).

35 Okesola, B. O., Suravaram, S. K., Parkin, A. & Smith, D. K. Selective Extraction and in situ Reduction of Precious Metal Salts from Model Waste to Generate Hybrid Gels with Embedded Electrocatalytic Nanoparticles. *Angew. Chem. Int. Ed.*, **55**, 183-187 (2016).

36 Slavik, P., Kurka, D. W. & Smith, D. K. Palladium-scavenging Self-assembled Hybrid Hydrogels – Reusable Highly-active Green Catalysts for Suzuki-Miyaura Cross-Coupling Reactions. *Chem. Sci.*, **9**, 8673-8681 (2019)

37 Vieira, V. M. P., Hay, L. L. & Smith, D. K. Multi-Component Hybrid Hydrogels – Understanding the Extent of Orthogonal Assembly and its Impact on Controlled Release. *Chem. Sci.*, **8**, 6981-6990 (2017).

38 Vieira, V. M. P., Lima, A. C., de Jong, M. & Smith, D. K. Commercially Relevant Orthogonal Multi-Component Supramolecular Hydrogels for Programmed Cell Growth. *Chem. Eur. J.*, **24**, 15112-15118 (2018).

39 Chen, F., Chen, C., Zhu, L., Tang, Z., Li, Q., Qin, G., Yang, J., Zhang, Y., Ren, B., & Zheng, J. General Strategy to Fabricate Strong and Tough Low-Molecular-Weight Gelator-Based Supramolecular Hydrogels with Double Network Structure. *Chem. Mater.*, **30**, 1743-1754 (2018).

40 Yu, X., Chen, L., Zhang, M. & Yi, T. Low-Molecular-Mass Gels Responding to Ultrasound and Mechanical Stress: Towards Self-Healing Materials, *Chem. Soc. Rev.* **43**, 5346-5371 (2014).

41 Yang, Y & Urban, M. W. Self-Healing Polymeric Materials, *Chem. Soc. Rev.* **42**, 7446-7467 (2013).

42 Lan, Y., Corradini, M. G., Weiss, R. G., Raghavan, S. R. & Rogers, M. A. To Gel or not to Gel: Correlating Molecular Gelation with Solvent Parameters. *Chem. Soc. Rev.*, **44**, 6035-6058 (2015).

43 Wang, Q., Mynar, J. L., Yoshida, M., Lee, E., Lee, M., Okuro, K., Kinbara, K. & Aida, T. High-Water-Content Mouldable Hydrogels by Mixing Clay and a Dendritic Molecular Binder. *Nature*, **463**, 339-343 (2010).

44 Nandi, S. K., Maji, K. & Haldar, D. Self-Healing Hydrogel from a Dipeptide and HCl Sensing. *ACS Omega*, **3**, 3744-3751 (2018)

45 Li, J., Geng, L., Wang, G., Chu, H. & Wei, H. Self-Healable Gels for Use in Wearable Devices. *Chem. Mater.*, **29**, 8932-8952 (2017).

46 Sharma, B., Singh, A., Sarma, T. K., Sardana, N. & Pal, A. Chirality Control of Multi-Stimuli Responsive and Self-Healing Supramolecular Metallo-Hydrogels. *New J. Chem.*, **42**, 6427–6432 (2018).

47 Karan, C. K. & Bhattacharjee, M. Self-Healing and Moldable Metallogels as the Recyclable Materials for Selective Dye Adsorption and Separation. *ACS Appl. Mater. Interfaces*, **8**, 5526–5535 (2016).

48 Yan, L., Shen, L., Lv, M., Yu, W., Chen, J., Wang, S., Fu, X. & Ye, Z. Self-Healing Supramolecular Heterometallic Gels Based on the Synergistic Effect of the Constituent Metal Ions. *Chem. Commun.*, **51**, 17627–17629 (2015).

49 Feldner, T., Hä, M., Saha, S., Esquena, J., Banerjee, R. & Díaz Díaz, D., Supramolecular Metallogel that Imparts Self-Healing Properties to Other Gel Networks. *Chem. Mater.*, **28**, 3210-3217 (2016).

50 Lovrak, M., Picken, S. J., Eelkema, R. & van Esch, J. H. Supramolecular Gluing of Polymeric Hydrogels. *ChemNanoMat*, **4**, 772-775 (2018).

51 Bera, S., & Haldar, D. A Rechargeable Self-Healing Safety Fuel Gel. *J. Mater. Chem. A*, **4**, 6933–6939 (2016).

52 Gross, B. C., Erkal, J. L., Lockwood, S. Y., Chen, C. & Spence, D. M. Evaluation of 3D Printing and its Potential Impact on Biotechnology and the Chemical Sciences. *Anal. Chem.*, **86**, 3240-3253 (2014).

53 Jungst, T., Smolan, W., Schacht, K., Scheibel, T & Groll, J. Strategies and Molecular Design Criteria for 3D Printable Hydrogels, *Chem. Rev.* **116**, 1496-1539 (2016).

54 Moroni, L., Burdick, J. A., Highley, C., Lee, S. J., Morimoto, Y., Takeuchi, S. & Yoo, J. J. Biofabrication Strategies for 3D in vitro Models and Regenerative Medicine. *Nat. Rev. Mater.* **3**, 21-37 (2018).

55 Yang, H., Zhang, S., Liu, K. & Fang, Y. Calix[4]arene-Based Low Molecular Mass Gelators to Form Gels in Organoalkoxysilanes. *RSC Adv.*, **6**, 109969–109977 (2016).

56 Nolan, M. C., Fuentes Caparrós, A. M., Dietrich, B., Barrow, M., Cross, E. R., Bleuel, M., King, S. M. & Adams, D. J. Optimising Low Molecular Weight Hydrogels for Automated 3D Printing. *Soft Matter*, **13**, 8426-8432 (2017).

57 Wei, Q., Xu, M., Liao, C., Wu, Q., Liu, M., Zhang, Y., Wu, C., Cheng, L. & Wang, Q. Printable Hybrid Hydrogel by Dual Enzymatic Polymerization with Superactivity. *Chem. Sci.*, **7**, 2748–2752 (2016).

58 Carlini, R., Toma, E., Odell, P. G. & Banning, J. H. Phase Change Inks containing Curable trans-1,2-Cyclohexane bis(urea-urethane) Compounds. *US Patent*, 7,153,349 (2006).

59 Chopra, N., Chretien, M. N., Keoshkerian, B., Eliyahu, J., Vanbesien, D. W. & Godedama, A. Curable Inks Comprising Bis-urea Gelators. *US Patent*, 9,328,248 (2016).

60 Liu, K., Zang, S., Xue, R., Yang, J., Wang, L., Huang, J. & Yan, Y. Coordination-Triggered Hierarchical Folate/Zinc Supramolecular Hydrogels Leading to Printable Biomaterials, *ACS Appl. Mater. Interfaces* **10**, 4530-4539 (2018).

61 Biswas, A., Malferran, S., Kalaskar, D. M. & Das, A. K. Arylboronate Esters Mediated Self-Healable and Biocompatible Dynamic G-Quadruplex Hydrogels as Promising 3D-Bioinks, *Chem. Commun.* **54**, 1778-1781 (2018).

62 Zhong, R., Tang, Q., Wang, S., Zhang, H., Zhang, F., Xiao, M., Man, T., Qu, X., Li, L., Zhang, W. & Pei, H. Self-Assembly of Enzyme-Like Nanofibrous G-Moleular Hydrogel for Printed Electrochemical Sensors, *Adv. Mater.* **30**, 1706887 (2018).

63 Rossi, S., Puglisi, A. & Benaglia, M. Additive Manufacturing Technologies: 3D Printing in Organic Synthesis, *ChemCatChem* **10**, 1512-1525 (2018).

64 Kitson, P. J., Marie, G., Francoia, J.-P., Zalesskiy, S. S., Sigerson, R. C., Mathieson, J. S. & Cronin L. Digitization of Multistep Organic Synthesis in Reactionware for On-demand Pharmaceuticals, *Science* **359**, 314-319 (2018).

65 Brown, T. E. & Anseth, K. S. Spatiotemporal Hydrogel Biomaterials for Regenerative Medicine. *Chem. Soc. Rev.*, **46**, 6532-6552 (2017).

66 Dubal, D. P., Chodankar, N. R., Kim D. H. & Gomez-Romero, P. Towards Flexible Solid-State Supercapacitors for Smart and Wearable Electronics. *Chem. Soc. Rev.*, **47**, 2065-2129 (2018).

67 Lu, W., Le, X. Zhang, J., Huang, Y & Chen, T. Supramolecular Shape Memory Hydrogels: A New Bridge Between Stimuli-Responsive Polymers and Supramolecular Chemistry. *Chem. Soc. Rev.*, **46**, 1284-1294 (2017).

68 Eastoe, J., Sánchez-Dominguez, M., Wyatt, P. & Heenan, R. K. A Photo-Responsive Organogel. *Chem. Commun.*, 2608–2609 (2004).

69 de Jong, J. J. D., Hania, P. R., Pugžlys, A., Lucas, L. N., de Loos, M., Kellogg, R. M., Feringa, B. L., Duppen, K. & van Esch, J. H. Light-Driven Dynamic Pattern Formation. *Angew. Chem. Int. Ed.*, **44**, 2373–2376 (2005).

70 Lee, S., Oh, S., Lee, J., Malpani, Y., Jung, Y.S., Kang, B., Lee, J. Y., Ozasa, K., Isoshima, T., Lee, S. Y., Hara, M., Hashizume D. & Kim, J. M. Stimulus-Responsive Azobenzene Supramolecules: Fibers, Gels and Hollow Spheres. *Langmuir*, **29**, 5869-5877 (2013).

71 Matsumoto, S., Yamaguchi, S., Ueno, S., Komatsu, H., Ikeda, M., Ishizuka, K., Iko, Y., Tabata, K. V., Aoki, H., Ito, S., Noji, H. & Hamachi, I. Photo Gel-Sol/Sol-Gel Transition and its Patterning of a Supramolecular Hydrogel as Stimuli-Responsive Biomaterials. *Chem. Eur. J.* **14**, 3977–3986 (2008).

72 Komatsu, H., Tsukiji, S., Ikeda, M. & Hamachi, I. Stiff, Multistimuli-Responsive Supramolecular Hydrogels as Unique Molds for 2D/3D Microarchitectures of Live Cells. *Chem. Asian J.*, **6**, 2368-2375 (2011).

73 Raeburn, J., McDonald, T. O. & Adams, D. J. Dipeptide Hydrogelation Triggered by Ultraviolet Light. *Chem. Commun.* **48**, 9355–9357 (2012).

74 Maity, C., Hendriksen, W. E., van Esch, J. H. & Eelkema, R. Spatial Structuring of a Supramolecular Hydrogel by Using a Visible-Light Triggered Catalyst. *Angew. Chem. Int. Ed.*, **54**, 998–1001 (2015).

75 Li, X., Fei, J., Xu, Y., Li, D., Yuan, T., Li, G., Wang, C. & Li, J. A Photoinduced Reversible Phase Transition in a Dipeptide Supramolecular Assembly. *Angew. Chem. Int. Ed.*, **57**, 1903-1907 (2017).

76 Tung, S.-T., Cheng, H.-T., Inthasot, A., Hsueh, F.-C., Gu, T.-J., Yan, P.-C., Lai, C.-C., & Chiu, S.-H. Interlocked Photo-degradable Macrocycles Allow One-Off Photo-triggerable Gelation of Organo- and Hydrogelators. *Chem. Eur. J.*, **24**, 1522-1527 (2017).

77 Roth-Konforti, M. E., Comune, M., Halperin-Sternfeld, M., Grigoriants, I., Shabat & D., Adler-Abramovich, L. UV Light-Responsive Peptide-Based Supramolecular Hydrogel for Controlled Drug Delivery. *Macromol. Rapid Comm.*, 1800588 (2018).

78 van Herpt, J. T., Stuart, M. C. A., Browne, W. R. & Feringa, B. L. A Dithienylethene-Based Rewritable Hydrogelator. *Chem. Eur. J.*, **20**, 3077–3083 (2014).

79 Lee, J. H., Jung, S. H., Lee, S. S., Kwon, K.-Y., Sakurai, K., Jaworski, J. & Jung, J. H. Ultraviolet Patterned Calixarene-Derived Supramolecular Gels and Films with Spatially Resolved Mechanical and Fluorescent Properties. *ACS Nano*, **11**, 4155–4164 (2017).

80 Draper, E. R., Schweins, R., Akhtar, R., Groves, P., Chechik, V., Zwijnenburg, M. A. & Adams, D. J. Reversible Photoreduction as a Trigger for Photoresponsive Gels. *Chem. Mater.*, **28**, 6336–6341 (2016).

81 Moriyama, M., Mizoshita, N., Yokota, T., Kishimoto, K. & Kato, T. Photoresponsive Anisotropic Soft Solids: Liquid Crystalline Physical Gels Based on a Chiral Photochromic Gelator. *Adv. Mater.*, **15**, 1335–1338 (2003).

82 Moriyama, M., Mizoshita, N. & Kato, T. Photopattering of Discotic Liquid Crystalline Gels. *Polym. J.*, **36**, 661–664 (2004).

83 Cornwell, D. J., Okesola, B. O. & Smith, D. K. Multidomain Hybrid Hydrogels: Spatially Resolved Photopatterned Synthetic Nanomaterials Combining Polymer and Low-Molecular-Weight Gelators. *Angew. Chem. Int. Ed.*, **53**, 12461–12465 (2014).

84 Chivers, P. R. A. & Smith, D. K. Spatially-Resolved Soft Materials for Controlled Release – Hybrid Hydrogels Combining a Robust Photo-activated Polymer Gel with an Interactive Supramolecular Gel. *Chem. Sci.* **8**, 7218-7227 (2017).

85 Cornwell, D. J., Daubney, O. J. & Smith, D. K. Photopatterned Multidomain Gels: Multi-Component Self-Assembled Hydrogels Based on Partially Self-Sorting 1,3:2,4-Dibenzylidene-D-Sorbitol Derivatives. *J. Am. Chem. Soc.*, **137**, 15486-15492 (2015).

86 Draper, E. R., Eden, E. G. B., McDonald, T. O. & Adams, D. J. Spatially Resolved Multicomponent Gels. *Nat. Chem.*, **7**, 848–852 (2015).

87 Che, X., Bai, B., Zhang, T., Zhang, C., Zhang, C., Zhang, P., Wang, H. & Li, M. Gelation Behaviour and Gel Properties of Two-Component Organogels Containing a Photoresponsive Gelator. *New J. Chem.,* **41**, 8614-8619 (2017).

88 Amabilino, D. J., Smith, D. K. & Steed, J. W. Supramolecular Materials. *Chem. Soc. Rev.*, **46**, 2404-2420 (2017).

89 Tantakitti, F., Boekhoven, J., Wang, X., Kazantsev, R. V., Yu, T., Li, J., Zhuang, E., Zandi, R., Ortony, J. H., Newcomb, C. J., Palmer, L. C., Shekhawat, G. S., de la Cruz, M. O., Schatz, G. C. & Stupp, S. I. Energy Landscapes and Functions of Supramolecular Systems. *Nat. Mater.*, **15**, 469-476 (2016).

90 Li, J.-L., Zhang, Z.-S. & Liu, X.-Y. in *Molecular Gels: Structure and Dynamics*, (ed. Weiss, R. G.) 88-128 (Royal Society of Chemistry, Cambridge, 2018).

91 Lovrak, M., Hendriksen, W. E. J., Maity, C., Mytnyk, S., van Steijn, V., Eelkema, R. & van Esch, J. H. Free-Standing Supramolecular Hydrogel Objects by Reaction-Diffusion. *Nat. Commun.*, **8**, 15317 (2017).

92 Ruíz-Olles, J. & Smith, D. K. Diffusion Across a Gel-Gel Interface – Molecular-Scale Mobility of Self-Assembled 'Solid-Like' Gel Nanofibres in Multi-Component Supramolecular Organogels. *Chem. Sci.*, **9**, 5541-5550 (2018).

93 Jaggers, R. W. & Bon, S. A. F. Temporal and Spatial Programming in Soft Composite Hydrogel Objects. *J. Mater. Chem. B*, **5**, 7491-7495 (2017).

94 Vigier-Carrière, C., Boulmedais, F., Schaaf, P. & Jierry, L. Surface-Assisted Self-Assembly Strategies Leading to Supramolecular Hydrogels. *Angew. Chem. Int. Ed.*, **57**, 1448-1456 (2018).

95 Yang, B., Adams, D. J., Marlow, M. & Zelzer, M. Surface-Mediated Supramolecular Self-Assembly of Protein, Peptide, and Nucleoside Derivatives: From Surface Design to the Underlying Mechanism and Tailored Functions, *Langmuir*, **34**, 15109-15125 (2018).

96 Raeburn, J., Alston, B., Kroeger, J., McDonald, T. O., Howse, J. R., Cameron, P. J. & Adams, D. J. Electrochemically Triggered Spatially and Temporally Resolved Multi-Component Gels. *Mater. Horiz.*, **1**, 241–246 (2014).

97 Piper, A., Alston, B. M., Adams, D. J. & Mount, A. R. Functionalised Microscale Nanoband Edge Electrode (MNEE) Arrays: The Systematic Quantitative Study of Hydrogels Grown on Nanoelectrode Biosensor Arrays for Enhanced Sensing in Biological Media. *Faraday Discuss.*, **210**, 201-217 (2018).

98 Tam, A. Y.-Y. & Yam, V. W.-W. Recent Advances in Metallogels. *Chem. Soc. Rev.*, **42**, 1540-1567 (2013).

99 Olive, A. G. L., Abdullah, N. H., Ziemecka, I., Mendes, E., Eelkema, R. & van Esch, J. H. Spatial and Directional Control over Self-Assembly using Catalytic Micropatterned Surfaces. *Angew. Chem. Int. Ed.*, **53**, 4132–4136 (2014).

100 Williams, R. J., Smith, A. M., Collins, R., Hodson, N., Das, A. K. & Ulijn, R. V. Enzyme-Assisted Self-Assembly Under Thermodynamic Control. *Nat. Nanotechnol.*, **4**, 19–24 (2009).

101 Conte, M. P., Lau, K. H. A. & Ulijn, R. V. Biocatalytic Self-Assembly Using Reversible and Irreversible Enzyme Immobilisation. *ACS Appl. Mater. Interfaces*, **9**, 3266–3271 (2017).

102 Zelzer, M., Todd, S. J., Hirst, A. R., McDonald, T. O. & Ulijn, R. V. Enzyme Responsive Materials: Design Strategies and Future Developments. *Biomater. Sci.*, **1**, 11-39 (2013).

103 Fores, J. R., Mendez, M. L. M., Mao, X., Wagner, D., Schmutz, M., Rabineau, M., Lavalle, P., Schaaf, P., Boulmedais, F. & Jierry, L. Localized Supramolecular Peptide Self-Assembly Directed by Enzyme-Induced Proton Gradients. *Angew. Chem. Int. Ed.*, **56**, 15984-15988 (2017).

104 Spitzer, D., Marichez, V., Formon, G. J. M., Besenius, P. & Hermans, T. M. Surface-Assisted Self-Assembly of a Hydrogel by Proton Diffusion. *Angew. Chem. Int. Ed.*, **57**, 11349-11353 (2018).

105 Marciel, A. B., Tanyeri, M., Wall, B.D., Tovar, J. D., Schroeder, C. M. & Wilson, W. L. Fluidic-Directed Assembly of Aligned Oligopeptides with π-Conjugated Cores. *Adv. Mater.*, **25**, 6398-6404 (2013)

106 Seibt, S., With, S., Bernet, A., Schmidt, H. W. & Förster, S. Hydrogelation Kinetics Measured in a Microfluidic Device with in Situ X-ray and Fluorescence Detection. *Langmuir*, **34**, 5535-5544 (2018).

107 Sevim, S., Sorrenti, A., Franco, C., Furukawa, S., Pané, S., deMello, A. J. & Puigmartí-Luis, J. Self-assembled Materials and Supramolecular Chemistry within Microfluidic Environments: From Common Thermodynamic States to Non-Equilibrium Structures. *Chem. Soc. Rev.*, **47**, 3788-3803 (2018).

108 Inostroza-Brito, K. E., Collin, E., Siton-Mendelson, O., Smith, K. H., Monge-Marcet, A., Ferreira, D. S., Rodríguez, R. P., Alonso, M., Rodríguez-Cabello, J. C., Reis, R. L., Sagués, F., Botto, L., Bitton, R., Azevedo, H. S. & Mata, A. Co-Assembly, Spatiotemporal Control and Morphogenesis of a Hybrid Protein-Peptide System. *Nat. Chem.* **7**, 897–904 (2015).

109 Mendoza-Meinhardt, A., Botto, L. & Mata, A. A Fluidic Device for the Controlled Formation and Real-Time Monitoring of Soft Membranes Self-Assembled at Liquid Interfaces. *Sci. Rep.* **8**, 2900 (2018).

110 Hedegaard, C. L., Collin, E. C., Redondo-Gómez, C., Nguyen, L. T. H., Ng, K. W., Castrejón-Pita, A. A., Castrejón-Pita, J. R. & Mata, A. Hydrodynamically Guided Hierarchical Self-Assembly of Peptide-Protein Bioinks. *Adv. Funct. Mater.* **28**, 1703716 (2018).

Acknowledgements

D.K.S. acknowledges EPSRC for funding (EP/P03361X/1). P.R.A.C. acknowledges funding from EPSRC and University of York (DTA award).

Author Contributions

P. R. A. C. and D. K. S. carried out the literature search and the writing of the article. D. K. S. led the process of editorial revisions.

Competing interests statement

The authors declare no competing interests.

Figure captions

Figure 1. A schematic of supramolecular gel assembly and strategies to achieve shaping and patterning of self-assembled gels. **a**, LMWGs form bulk gels through hierarchical self-assembly. On application of an appropriate trigger, individual gelator molecules assemble through non-covalent interactions to form fibrils, which subsequently bundle together to form wider nanofibres. Nanofibre entanglement results in the formation of a sample-spanning solid-like network and gelation. **b**, Self-standing gels can maintain a pre-defined shape. Structured gels have different compositions and hence behaviour patterned into different domains. **c**, These concepts can combine to form gels that are both shaped and structured. **d**, An increase of LMWG loading causes an increase in network density (left). This strategy can generate gels that form intricate self-standing sculptures. A change in solvent may cause an increase in the solid-like nature of the gel – rheological studies have shown solvent tuning can make gels both stiffer and stronger, as can optimising the solubility of the gelator in the solvent system of choice (middle). The LMWG can be reinforced with a polymer gel network (right). Panel **c** (left) is adapted with permission from REF. 17, Wiley-VCH. Panel **c** (middle) is adapted with permission from REF. 15, Wiley-VCH. Panel **c** (right) is adapted with permission from REF. 110, Wiley-VCH.

Figure 2. Some supramolecular gels formed from low-molecular-weight gelators (LMWGs) are thixotropic as a consequence of molecular-scale mobility of the gel-forming components. a, Dissolved LMWGs can heal damaged nanofibres to reform the sample-spanning gel network. **b**, Under low shear, self-healing gels have G' (storage modulus) > G" (loss modulus) and are solid-like gels, but under high shear G" > G' and they behave as liquids. On removal of high shear, a self-healing gel rapidly recovers its gel-like rheological properties. **c**, Incorporation of a small quantity of a self-healing gel (5-20%) can impart thixotropic performance onto a non-healing gel. Panel **b** is adapted with permission from REF. 48, Royal Society of Chemistry. Panel **c** is adapted with permission from REF. 49, American Chemical Society.

Figure 3. Two approaches to 3D-printing of supramoleular gels. a, Direct printing of a thixotropic gel using its self-healing properties, with the gel converting to a sol on injection and then reforming a gel. The photographs illustrate examples where gels loaded with different dyes are printed adjacent to one another (left) and on top of each other (right). **b**, Combining LMWG and polymer gelators in multi-component gels allows an LMWG to be printed into a shape, which is then modified using photolithography to yield the polymer gel network, giving a more robust and permanent structure. The photographs illustrate combined 3D-printed hybrid LMWG/PG gels. Panel **a** is adapted with permission from REF. 56, Royal Society of Chemistry. Panel **b** is adapted with permission from REF. 57, Royal Society of Chemistry.

Figure 4. Structuring of gels using photo-patterning methods. a, There are two methods of photo-patterning, namely, light-induced formation of gel (left) and light-induced breakdown of gel (right). **b**, Trans-cis isomerisation of UV-active groups such as azobenzenes and fumaric amides can induce gel-sol transitions. Use of photomasks (or laser irradiation methods) allow all these transitions to be performed with spatial control in 2D or 3D. **c**, Photo-acid generators have been used to form spatially-resolved gel structures by triggering the protonation of the low-molecular-weight gelator (LMWG). Panel **b** (top) is adapted with permission from REF. 70, American Chemical Society. Panel **c** (bottom) is adapted with permission from REF. 71, Wiley-VCH.

Figure 5. Photopatterning of multi-component and multi-domain gels. a, Photopatterning can be achieved either by positive writing in which one gel network is assembled within another, or negative writing in which two self-sorted gel networks are formed simultaneously and then one network is etched away. **b**, Combining a low-molecular-weight gelator (LMWG) with a UV-polymerisable polymer gelator (PG) allows gels to be formed with properties of both networks, typically responsiveness (attributed to the LMWG) and robustness (attributed to the PG). Systems can be patterned to have domains with different compositions and hence physical properties – for example, the LMWG network is soft and the combined LMWG/PG network is robust. If the LMWG is capable of controlled release, these properties are incorporated into the shaped object – for example the gel stripe shows directional release of an acid-functionalised pharmaceutical (naproxen) depending on the pH values of the two different receiving compartments. **c**, Patterning multidomain LMWG/LMWG gels has been achieved in positive writing mode with the second photo-irradiation step being used to assemble the DBS-Gly network and negative writing (etching) mode in which the UV-Vis irradiation is used to isomerise and hence disassemble the stilbene gelator network. Panel **b** (top) is adapted with permission from REF. , Wiley-VCH. Panel **b** (bottom) is adapted with permission from REF. 84, Royal Society of Chemistry.

Panel **c** (top) is adapted with permission from REF. 85, American Chemical Society. Panel **c** (bottom) is adapted from REF. 86, Springer Nature Limited.

Figure 6. Diffusion control of reactive components can yield patterned gels. **a** Diffusion of acyl hydrazone (H) and aldehyde (A) from different locations in an alginate gel enables the spatially controlled formation of a shaped tris-hydrazone gel. **b**, General method of preparing free-standing objects using the cutting approach. (1) An alginate hydrogel is prepared in a Petri dish. (2) An arbitrary shape is cut out of the alginate. (3) Solutions of hydrazide **H** (green) and aldehyde **A** (blue) are placed into the reservoirs. (4) The hydrazide and aldehyde diffuse through the alginate matrix and react at the diffusion fronts to form a tris-hydrazone gelator, which then self-assembles into a gel structure (yellow). (5) The remaining solutions are removed. (6) A solution of EDTA is poured into the Petri dish until it completely covers the alginate containing the formed pattern. (7) After all alginate is dissolved (as observed by visual inspection), the remaining solution is removed and the free-standing hydrogel object is obtained. **c**, A two-component gels comprising acid and amine functions have been shown to exchange across a gel-gel interface, leading to the establishment of chemical gradients in gel composition. In this case, amine 1 is fluorescent, while amine 2 is not, and the diffusion exchange across the interface can be visually monitored over time under UV-irradiation. Panels **a** and **b** are adapted from REF. 91, Springer Nature Limited. Panel **c** is adapted with permission from REF. 92, Royal Society of Chemistry.

Figure 7. Electrochemical surface patterning of self-assembled gels. a, Electrochemical activation of a naphthalene dipeptide hydrogel. The electrochemical oxidation of hydroquinone liberates two protons, which induce gelation by acidification. **b**, Control of the applied current at different locations can shape gels in 2D (top) and control gel height (bottom). Panel **b** is adapted from REF. 96, Royal Society of Chemistry.

Figure 8. Surface patterned gels assembled on patterned catalytic surfaces. a, Spatially-defined catalytic sites can enforce spatially-controlled formation of a self-assembling low-molecular-weight gelator **(**LMWG) from one or more pre-gelators with gel formation only occurring on the regions with catalytic sites. **b**, Micropatterned sulfonic acid sites catalyse the formation of tris-hydrazone hydrogels on the microscale by catalysing the reaction between acyl hydrazone and aldehyde. **c**, Immobilised thermolysin enzymes induced spatially-controlled microscale formation of an Fmoc-dipeptide LMWG. Panel **b** is adapted from REF. 99, Wiley-VCH. Panel **c** is adapted from REF. 100, Springer Nature Limited.