Faraday Discussions
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# Concluding remarks: *Faraday Discussions* on Advances in supramolecular gels

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These concluding remarks summarise the *Faraday Discussions* that was held in Glasgow, Scotland, on Advances in supramolecular gels, between the 30th of April and the 2nd of May 2025. The meeting was organised by Prof. Dave Adams (University of Glasgow, UK) and Prof. Annela Seddon (University of Bristol, UK) who co-chaired the meeting, in collaboration with the Scientific Committee, Prof. Krishna K. Damodaran (University of Iceland, Iceland), Prof. Demetra Giuri (University of Bologna, Italy) and Prof. Xuehai Yan (Chinese Academy of Science, China). The meeting was organised in four main sections over the four day programme. These were broadly devoted to the characterising (Session 1), using (Session 2), designing (Session 3) of supramolecular gels, and multicomponent gel systems (in Session 4). A lively poster session with range of posters presented mainly by early career, students and postdoctoral fellows, as well as some more established researchers, ran throughout the meeting. The *Faraday Discussions* programme had contribution talks that highlighted the research area from the design and synthesis of (supramolecular) gels, formed from small organic gelators and bioinspired structures and conjugates, to the different types of characterisation techniques employed for such soft-material research, including the use of rheology, scattering techniques and a variety of imaging platforms, as well as computational studies. This was also completed by the contributions on the applications of functional soft materials with both established and emerging applications. Herein, I will provide a short introductory remark on this fast-growing research field, and a short summary of the work presented within the four sessions, along with the associated discussions that took place. I will then conclude with a brief personal focused discussion of what I consider the main points raised throughout the meeting associated with some of the challenges that this fast-growing research area is facing.

## Introduction

Supramolecular chemistry has become a leading research area within chemistry. This is not least due to the intracapillary nature of the subject which encompasses a range of disciplines and research areas, resulting in the awarding of several

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high-profile prizes in chemistry over the last few decades. The fundamental of supramolecular chemistry is host–guest chemistry, where complimentarily and self-assembly processes are some of the key concepts, and universally applicable to supramolecular gels and soft-material formations. But the fact is that many supramolecular chemists started their research interests in gels with serendipitous discoveries! Hence, in the past, it was not uncommon to hear colleagues explain their early introductions to, and interest in, soft matter chemistry as having been initiated from their research group members knocking on their office doors to bring news of problems with isolation of compounds due to formation of gel-like materials (the author of this paper being one of them)! In fact, gels (or gel formation) could be looked at as being bit of a 'bugger' in the lab! My first experience being that of a fluorophore that we had functionalised with a dendric lysine residue… a structure that we could not purify by running a flash column on it as it 'gellated in organic solution'… leading to the formation of a highly green, fluorescent gel…. which 'withstood' the inversion test (now we would call that a 'functional gel')! But this was the catalyst for my interest in supramolecular gels and their applications! This is an area that has grown strongly over the years within the research community, who now employ a range of physical and spectroscopic characterisation techniques, microscopic imaging platforms and rheological analysis, to establish the physical and morphological nature of gels, and computational approaches to develop functional structures and materials. All this past work and discovery has contributed to our understanding of their physical and mechanical properties and importantly, their wide range of applications.

Nowadays, supramolecular gels, and the very related supramolecular polymer research, is high on the agenda within the supramolecular community, with many reviews and accounts having been written over the years.[1–4] Their rich chemistry, and their importance in a range of applications are becoming more and more apparent.[5–7] This *Faraday Discussions* meeting clearly manifested that view in my humble opinion, with several other such *Faraday Discussions* meetings having also been organised in the past, on the subject. The area of supramolecular gels has matured quickly, and this was very nicely highlighted in so many of the talks and in the following discussions over the three bright and sunny days in Glasgow. This *Faraday Discussions* meeting demonstrated that the future of supramolecular gel researcher is, without any doubt, bright! The key to its success has been the willingness of the research community to embrace and apply new technologies and characterisation techniques and look beyond the boundaries of classical chemistry research and engage in cross- and multi-discipline driven research endeavours. The take-home message from this current meeting certified that opinion in my mind.

## Spiers Memorial Lecture

The meeting was opened by the Spiers Memorial Lecture delivered by Prof. Darrin Pochan (University of Delaware, USA, **https://doi.org/10.1039/D5FD00044K**) and chaired by Prof. Dave Adams (University of Glasgow, UK). Prof. Pochan gave a good introduction to the concept of supramolecule gels, and the range of binding interactions employed in the formation of such structures from weak non-covalent interactions, focusing mostly on the generation of supramolecular

hydrogel networks. The lecture also gave an historic perspective, which was followed by an overview of Prof. Pochan's research in the area to date, with emphasis on how 'it all started' and the importance of close and long-standing collaborations on delivering the research work, and the importance of engaging with experts in other disciplines to successfully deliver on such work. This discussion was then followed by an overview of some recent developments within the area (spanning *ca.* the last five years or so), making direct reference to some of the work of those presenting at this *Faraday Discussions* meeting.

The Spiers Memorial Lecture set the bar for this meeting, Prof. Pochan discussed the complexity of molecular folding and the formation of higher order structures; how different kinetics can be employed to self-assemble gels and the effect of ion concentrations, *etc*, such as in the formation of healing network-injectable solid hydrogels. Particular emphasis was paid to characterisation of hydrogels, such as using state-of-the-art imaging platforms, which allows for better morphological analysis, and the use of rheological and scattering techniques; the latter being of major help in determining the homogeneity of the self-assembly. This was emphasised by many of the other presenters, as well as in the general discussions at this meeting. Prof. Pochan stressed that characterisation is now focusing on gaining information of what the exact nanostructure looks like, which was nicely highlighted. This will lead to better design and consequent applications, and that understanding the pathway dependence (responsiveness) of the supramolecular structure, is and will be, a key feature in any such future developments.[8,9] Referring to '*Jello Fruit Cake Desserts*' Prof. Pochan highlighted the necessity of thinking outside the normal gelation approaches, and looking towards making functional gels, by 'mixing things into gels' by incorporation of structures, by means of encapsulation' of a range of materials, such as proteins, *etc.*,[10] for delivery purposes, *etc*. The idea of combining classical (covalent) polymer chemistry with the supramolecular approach, was referred to as the 'best of both worlds', particularly from the point of developing mechanically robust systems. Network properties within multicomponent systems are particularly relevant to 3D printing of gel structures; but this I believe has relevance to the creation of purposefully designed materials for environmentally responsive and targeted functions.[11]

The unpredictability of self-assembly processes, and that in most cases researchers cannot anticipate the outcome except by carrying out the measurements, was flagged! This again was also brought up by many of the speakers in the following sessions, as well as during the discussions. Another issue was reproducibility, which is often difficult to achieve within supramolecule gel formations. However, the fact that computational design of supramolecular systems has become more accessible, and that both AI and machine learning for designing specific molecular assembly functions, is now much more accessible, will, without any doubt, have a major impact on being able to tune the assembly formation into different nanostructures within gels.

Nanostructures controlled by chirality were also discussed. As chirality plays a major part in life, changing the stereochemistry within supramolecular gels (ligand structures) can also have a major effect on the self-assembly outcome (as my lab has recently demonstrated[12]), there needs to be more rationalisation around this fact. Finally, the issue of, 'self-assembly pathways' and 'will we be able

to predict the outcome of self-assembly formations?', was mentioned, a question/topic that surfaced many times throughout this *Faraday Discussions* meeting.



### Session 1: Characterising supramolecular gels

The first session of this *Faraday Discussions* meeting focused on the concept of *characterisation*. This session comprised six papers spanning over two days and was chaired by Prof. Annela Seddon (University of Bristol, UK), and opened by Prof. Vince Conticello (Emory University, USA) who presented work on the self-assembly of surfactant-like peptides in aqueous solution, which are formed from facile self-assembly of peptides possessing hydrophilic and hydrophobic residues, forming supramolecular hydrogels (**https://doi.org/10.1039/D4FD00190G**). The peptides studied, were the bola-amphiphilic peptides Ac-KLIIIK-$NH_2$ and Ac-KIIILK-$NH_2$, that give rise to the formation of self-assembly, with morphology consisting of nanosheet and nanotube formations, respectively, despite their related structural features. The self-assembly formation was characterised using a range of spectroscopic techniques, imaging platforms, and scattering measurements, which included the use of small-angle neutron scattering (SANS). The formation of the nanotubes was proposed to occur *via* a monolayer model, the morphology of which was probed by using TEM, as was the morphology of the nanosheets which consisted of ribbon-like assemblies with a range of diameters and lengths. Both systems were also investigated using synchrotron small-angle (SAXS) and wide-angle X-ray scattering (WAXS) techniques using solution-based samples of the peptide assemblies; the outcome of these measurements confirming the morphological nature of the assemblies seen in the TEM imaging. And while the morphology of the two systems was quite different, it was concluded that their supramolecular structures were based 'on a common core', with computational analysis (using AlphaFold-Multimer and ZipperDB) predicting a parallel cross-β fibril to be the common constituent of both peptide assemblies: 'the amyloid-like behaviour' dominating 'the properties of these materials'. The cryo-EM analysis was also used to probe the mechanism for the peptide assembly formation at near-atomic resolution. The following discussion was in part centred on the structural nature of the two assemblies and the effect this has on the assembly outcome, the preparation of the samples and the use of the cryo-EM. An interesting discussion on the use of different methods to detect the amyloid structure, took place. The problem is that 'many papers' (in the literature) discuss folding as amyloid structures and that we might have to revisit the 'assumption' and define the oligomerisation processes taking place, where it was concluded that 'we might need to rethink more or less anything' when it comes to such assembly processes! Discussion on if and how, higher order formation of amyloid peptides assemblies, over extended time, was possible, and how such formation could be probed, took place; this coming on the back of a discussion on the formation of the observation from TEM, which often gave evidence of more ordered structures being observed after 2–3 weeks. The presentation and the paper were an excellent demonstration of the use of a range of measurements and experimental techniques to characterise the structural nature, and the self-assembly processes that peptide-based structures can undertake in the formation of hydrogels.

The above presentation was followed by Prof. Dimitra Katrantzi (University of Leeds, UK) (**https://doi.org/10.1039/D4FD00204K**) on the characterisation of peptide-based hydrogels using cryo-SEM. The presentation followed the above paper nicely, as it demonstrated the use of a range of experimental techniques, to elucidate both the structure and function of peptide-based hydrogels, formed using (photochemically) crosslinked globular BSA based hydrogels. The key message in Prof. Katrantzi's presentation was to address the problems associated with sample preparation and minimising artefacts in the use of the cryo-SEM, these often being associated with the sample preparation and the problem with non-reproducible results. The control was achieved using a new sample preparation method that consisted of *in situ* gelation, using high pressure freezing (HPF), plasma focused ion beam (pFIB) milling, sublimation, and low doses of secondary electron imaging. *Ex situ* samples of the BSA hydrogels were also prepared and analysed in a comparable manner to the *in situ* prepared samples. The results from the cryo-SEM characterisation were then compared to results previously obtained on such samples using small angle scattering (SAS) analysis. Rheology studies on the *in situ* gelled systems were also carried out. The results demonstrated that significant differences were observed for the two systems, as is evident from Fig. 1 (reproduced Fig. 4 from Prof. Katrantzi's contribution). As part of this session, the discussion that followed was focused on the use of a range of characterisation techniques and the need to obtain reliable and reproducible means of preparing gel samples and the analysis of these. Hence, the issue of sample preparation, the issue of reproducibility of peptide self-assembly formations, which is often difficult to demonstrate, and the use of different supplier, instruments and sample sizes

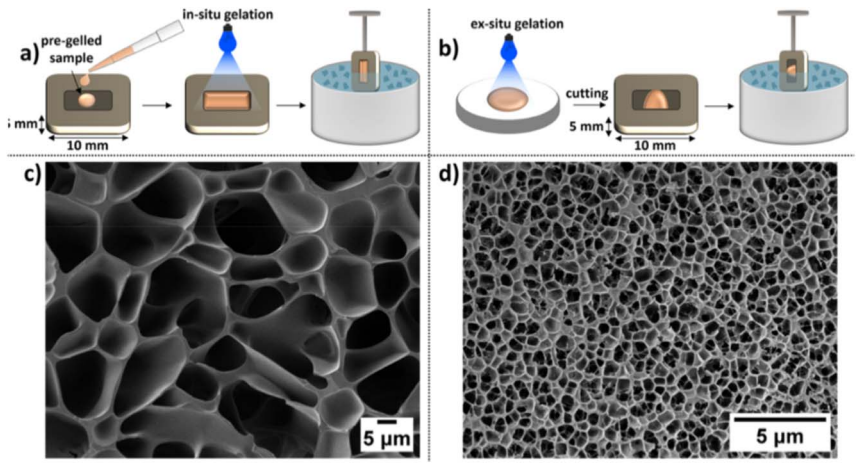


Fig. 1 (a and b) Schematic representation of the formation of the *in situ* and *ex situ* hydrogels, the latter involving gelling the sample in the cryo-holder before freezing in slush nitrogen. This formation overcomes the risk of potential structural change in the sample due to tearing or shearing. (c and d) The cryo-SEM images of the BSA hydrogels (7.4% BSA protein hydrogel) that were frozen in slush nitrogen and prepared by the *in situ* (c) and the *ex situ* protocols (d), respectively. Reproduced from https://doi.org/10.1039/D4FD00204K with permission from the Royal Society of Chemistry.

and how these can have an effect on the scientific outcome, was extensively discussed, as was the potential problem with the interpretation of cryo-SEM results – it was pointed out that these can often be wrong or even misleading in the literature.

The final lecture of the day was given by Prof. Gareth Lloyd (Lincoln University, UK), who, unlike the above lectures, focused on the synthesis of self-assembled structures that can lead to the formation of supramolecular polymers and a gel (as the end product) from small organic molecules through the use of reversible dynamic covalent chemistry (imine chemistry) (https://doi.org/10.1039/D5FD00016E). The initial imine formation between compounds **A** and **B** resulting in the potential reaction network formation, was followed by an enol–keto tautomerisation process, at alkaline pH in water, as shown in Fig. 2 (reproduced Scheme 1 from Prof. Loyd's contribution). This gives a supramolecular polymer as a single 'product' $\mathbf{C}^{n-}$ which is formed (its formation monitored by both HPLC and NMR) through the autocatalytic reaction (Fig. 2, as determined from extensive kinetic analysis and the formation of the S-curve), the other intermediates are not observed, possibly due to thermodynamic instability. Acidification of this species gives rise to the formation of a supramolecular gel; the process being described as 'autoinduction through the coupling of nucleation-dependent self-assembly of a supramolecular gelator'. The morphology of this system was probed by SEM demonstrating the formation of gel consisting of a fibrous network. The following discussion on this paper was on a range of topics, including how to connect an autocatalytic process with supramolecular polymerisation, and the gel formation. As well as, how does secondary nucleation affect the self-assembly process, and what was the

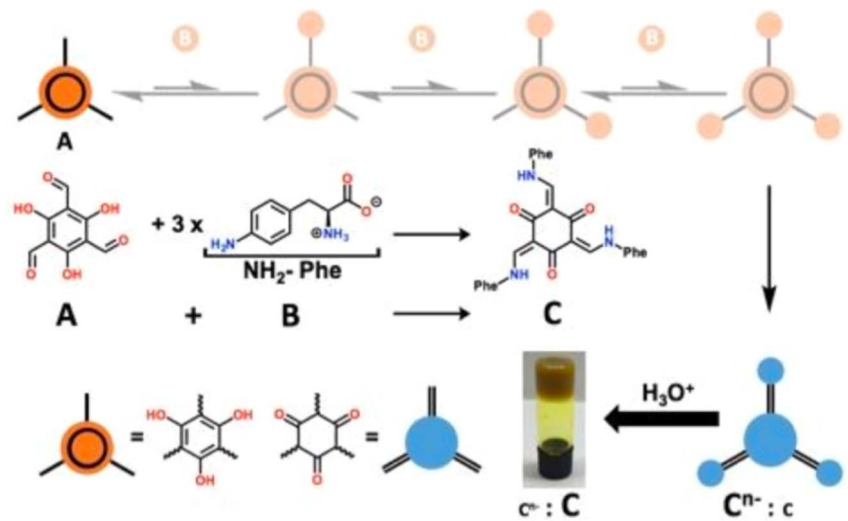


Fig. 2 Synthetic scheme showing the reaction between A and B in alkaline water, pH 8, which gives rise to the formation of deprotonated non supramolecular fibre structure $\mathbf{C}^{n-}$. Subsequent acidification of $\mathbf{C}^{n-}$ results in protonation and concomitant formation of the low molecular weight gelator **C**. Reproduced from https://doi.org/10.1039/D5FD00016E with permission from the Royal Society of Chemistry.

conformation of the imine within the initial product, and does the conformation affect the formation of the supramolecular product? This was followed by a discussion on the autocatalytic nature of the formation of the self-assembly; but the chemistry itself does not have to be?

The first session of this *Faraday Discussions* on supramolecular gels, concluded with the 'Lightning poster presentations', comprised of 12 one-minute presentations. The discussion then continued during the poster session, highlighting the 20 year anniversary of the Royal Society of Chemistry journal *Soft Matter*.

The second day of this session commenced with a presentation by Prof. Karen Edler (Lund University, Sweden) (**https://doi.org/10.1039/D5FD00004A**). The paper and the discussion focused on the development and the study of the liquid crystalline phases formed from the non-ionic amphiphiles phytantriol and monoolein, in excess water mixtures of: two protic ionic liquids, namely ethylammonium nitrate (EAN) and ethanolammonium nitrate (EtAN); and three deep eutectic solvents (DES), formed from mixtures of choline chloride with urea (ChCl:U), fructose or citric acid. Both phytantriol and monoolein are employed in a range of soft material formations, such as colloidal particles (cubosomes or hexosomes). The obtained gel systems have the properties of being biodegradable green solvents and have melting points below room temperature, and as such, provide good solubility for drugs and natural products. Phytantriol is the more toxic of the two, with monoolein often employed within cells. More importantly, the water does not evaporate from such systems, which often is the problem with lyotropic liquid crystal gels. The gels were characterised using small angle X-ray scattering at different water concentrations and at different temperatures. From these measurements, phase diagrams where obtained, where the phase behaviours were described as a quasi-ternary mixture. The study shows that EAN, EtAN as well as ChCl:U could all be incorporated into the lyotropic cubic phases of either phytantriol or monoolein. The following discussion on this paper focused in part on the importance of the solvent preparation, and how viscosity and temperature combination was a big factor, the SAXS studies, and the generation of the phase diagrams. From an application point of view, the use of such solvents to dissolve peptides was discussed, and that the polarity of these solvent systems could be probed using fluorescent probes.

The next paper presented was that of Prof. Joel Schneider (National Cancer Institute, USA) (**https://doi.org/10.1039/D5FD00018A**), who focused his paper and presentation on the temperature dependence of the self-assembly and folding of peptide amphiphiles based on β-hairpin amphiphiles (to give fibril structures), from the so called cold-denatured state, that could be used in the formation of hydrogels for clinical applications. The use of temperature dependent spectroscopic characterisation and computational analysis (this method being presented in the paper), allowed for the solvent-accessible hydrophobic (SAH) surface area to be determined for a range of amphiphilic β-hairpin peptides. This was proven to be critical in controlling the self-assembly, the study demonstrating that in comparison with peptides that have smaller SAH values, peptides that have large SAH values can both self-assemble at lower temperatures and at faster rates. The following discussion was lively and included questions on the possibility to gain control over the kinetics of the denaturation process, and if the same structure and morphology (self-assembled fibrils state) was always obtained following the denaturation process of such peptides. A very good discussion on the general 'rate

of assembly' as a function of temperature, and how such dependence can drive the self-assembly of soft materials down different assembly pathways, and how these can be controlled, took place.

The last presentation of this session was delivered by Prof. Edward Egelman (University of Virginia, USA), focusing on the use of cryogenic electron microscopy (cryo-EM) in the characterization of supramolecular gels at the atomic level (**https://doi.org/10.1039/D4FD00181H**), work that was carried out in collaboration with Prof. Dave Adams. While X-ray crystallography has been one of the most popular ways of exploring (self-assembly) molecules at the atomic level within the (supramolecular) community, the advent of the use of cryo-EM has changed that. The fact that this is now the most dominant technique used in structural biology demonstrates the power of this technique to visualise macrostructures, which is now also beginning to emerge as being used in the characterisation with 'near-atomic resolution' of systems such as peptide assemblies. The structure of gels, or their morphology is normally probed by using TEM or SEM imaging. Here, Prof. Egelman's in his contribution, used the well-known CarbIF dipeptide isoleucine–phenylalanine (IF) modified at the N-terminus, which is known to give rise to self-assembly gel formation, developed by Prof. Adams, to demonstrate the power of the cryo-EM. The results demonstrated the atomic structure of the tubular micelle formed by this dipeptide, at a high-atomic level, demonstrating the 'enormous potential for using cryo-EM. The cryo-EM map showing 7-start helical packing of the CarbIF micelle, enabling the researchers to deduce the mechanism for its formation. Prof. Egelman then went on to discuss the challenges that such imaging, such as associated with helical structures, can have in the analysis of self-assembly gels, and the pitfalls possible for helical assemblies when a near-atomic level of resolution is not reached. I felt this was a highly motivative lecture, where the use of relatively new and under-explored imaging platform within the area of supramolecular soft-material chemistry was put to the test with a very positive outcome. The discussion that followed this presentation was very much focused on the message given in the last reseeding sentence; where first, the use of cryo-EM for non-peptide structures was discussed, with the idea of using cryo-EM to interrogate the structures of supramolecular self-assembled polymers. The limitation of cryo-EM was also discussed, and what kind of molecular weights and assembly sizes this technique could be used to image, and likewise, if it could be used to exploring artefacts within self-assembly structures such as gels (with direct reference to the work carried out in Prof. Edward Egelman's contribution). In context with the contribution discussed, the need to generating large quantity data, and in fact 'how much data' we need to be able to make prediction was also considered and discussed. Sample preparation both of gels and peptide assembled (filaments) was also discussed and how images of these can be achieved along with other structures such as spherical systems, *e.g.* viruses, vesicles, and other particles. Overall, it was clear from the discussion that took place that cryo-EM is an important emerging technique that is of great value to understand structure and properties of self-assembled systems, but it might be less so available to be used to probe self-assembly pathways.

## Session 2: Using supramolecular gels

The second session of this *Faraday Discussions* meeting focused on the application of supramolecular gels and was chaired by Prof. Demetra Giuri (University of Bologna, Italy), with four discussion papers being assigned to this session. The first paper presented was that by Prof. Aline Miller (University of Manchester, UK), on investigating the co-assembly of amphipathic short peptides in the formation of peptide based hydrogels (**https://doi.org/10.1039/D5FD00036J**). The lecture focused on addressing the question of, if mixing together peptides of different chemical structures would lead to the formation of co-assembly or distinct fibrillar aggregated forms, does such mixing give rise to co-assembly or non-co-assembly formations? To address this, Prof. Miller used two types of peptides possessing a fluorophore and a quencher – (FITC-K-K$(FEFK)_2$K and Dabcyl-K-K$(FEFK)_2$K) – as shown in Fig. 3 (reproduced Fig. 1 from Prof. Miller's contribution), that could be used to probe the co-assembly formation through their Förster resonance energy transfer (FRET) pair formation. The addition of a third peptide – K$(FEFK)_2$K – lacking the fluorophore or the quencher (or the spacer connecting

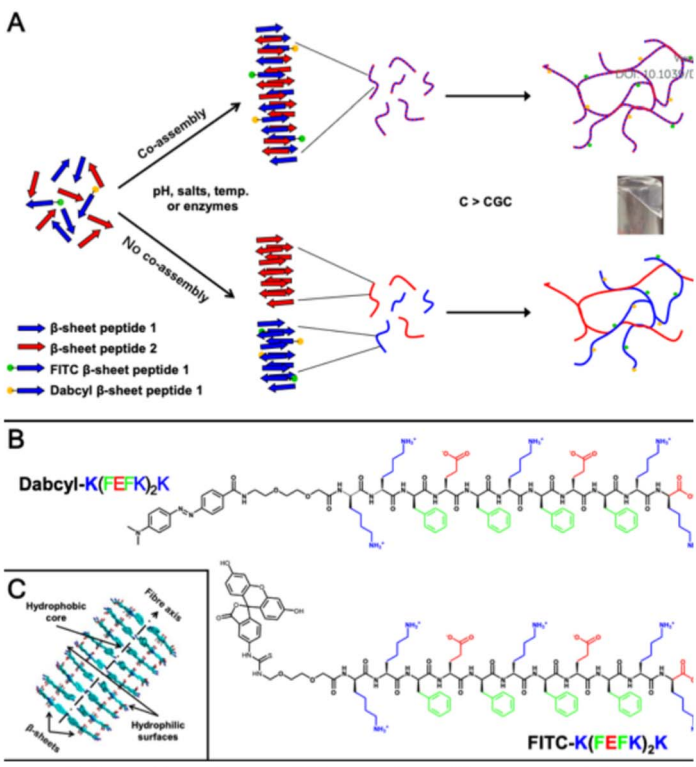


Fig. 3 (A) Cartoon describing the two different self-assembly pathways of the employed peptides giving rise to either a co-assembled peptide or not. (B) The chemical structure of the two peptides used bearing a quencher and a fluorophore for FRET analysis. (C) Schematic representation of the proposed β-sheet fibre molecular packing. Reproduced from https://doi.org/10.1039/D5FD00036J with permission from the Royal Society of Chemistry.

these to the peptides) to the hydrogel assembly of the two modified peptides, would then result in modulation of the FRET interaction depending on its association within the peptide hydrogel; this being observed by monitoring the changes in the fluorescence of the assembly. The presentation indeed showed that the use of a FRET pair to interrogate such assembly formation was possible. And that the nature of the peptide sequence was important. The discussion that followed was centred on the sample preparation (do they simply mix or do they co-assemble in a programmable manner?), the order of addition of the peptides in the hydrogel formation, their photophysical properties, which demonstrated that quenching occurs due to assembly formation; the work highlighted that dilution did not affect the quenching which indicated that such assembly formation occurred, (*e.g.* as depicted schematically in Fig. 3). The emission properties of the assembly were also investigated as a function of temperature. Discussion followed on the morphological nature of the hydrogel (which was formed from a single fibral network), and how this change modulated, depending on some of the above outlined (design) criteria, and the use of different stereochemistry within the peptide sequences, and stoichiometries of the peptide conjugates. The presentation and paper, clearly demonstrate the importance of applying strict design principles in the 'synthesis' of such co-assemblies, and the advantage of employing a range of spectroscopy and imaging platforms to elucidate such assembly formation, and the advantage of being able to probe photophysical properties of such assemblies, as this author has extensively employed to probe self-assembly of such structures, higher-order supramolecular assemblies, and pathways.[13–15]

The next paper presented in Session 2 was that of Prof. Herdeline Ann Ardoña (University of California, Irvine, USA), which was centred on forming multicomponent hydrogels, by developing supramolecular peptide dopants that could be employed in composite hydrogels to induce photoconductivity and mechanical tunability within digital light processable materials (**https://doi.org/10.1039/D5FD00031A**). The work was based on the synthesis of porphyrin systems, which had peptides conjugated to them through the tetra-phenyl moieties of the porphyrins. Such molecules can self-assemble into photoconductive nanostructures. Within the developed structures some of the peptides were functionalised with allyloxycarbonyl (alloc) groups, which allowed for their direct co-polymerisation as crosslinkers within the hydrogel matrix, while others were added as 'dopants' during the synthesis. This resulted in the formation of hybrid materials consisting of acrylate-based polymers and supramolecular peptide-based porphyrin assemblies; the latter functioning as the $\pi$-based photoconductive units. Special emphasis was put on elucidating the effect of doping digital light processing (DLP)-printable poly(ethylene glycol) diacrylate (PEGDA) gels, with these photoconductive structures. The physical properties of the developed hydrogel materials, including investigation of their rheology and morphology, were studied in aqueous solution at different pHs, and in the presence of salts. The assembly trigger was shown to be pH or $CaCl_2$ dependent, the morphology of these multicomponent hydrogels being very much affected by these two triggers. Using a range of spectroscopic techniques, the photophysical properties of the systems were probed. By radiating the gels it became apparent that different conditions affect the printability of the resulting hydrogels. The nature of the amino acids within the peptide conjugates was also shown to be important, as

well as the type of triggers employed; the use of both acid and $CaCl_2$ giving rise to self-assembly formation for all the peptides tested. All the systems had measurable conductivities under an applied voltage of 0.1 V. The following discussion was on a range of topics, which included discussion of the spectroscopic properties of the systems. These were probed in water, with some questions on the use of circular dichroism (CD), and its reliability to probe the degree of assembly formation of the developed porphyrins. Discussion on the sample and the gel preparation, and the use of excess $CaCl_2$, and how that affects the self-assembly itself, if other self-assembly formation, such as the formation of micellar systems could occur, the exploration of the photoconductivity properties, and if there was a direct connection between the structures and the peptide sequence, also took place.

Next up within this session was Prof. Meital Reches (Hebrew University of Jerusalem, Israel), who discussed the use of self-assembly and sol–gel synthesis in the development of new materials, where the emphasis was on the synthesis of silylated peptide sequences and their subsequent use in sol–gel polymerisation (**https://doi.org/10.1039/D5FD00014A**). Similarly to the previous paper, here the feasibility of combining self-assembly (non-covalent interactions) with the more classical covalent sol–gel formation was explored using two types of amino acids, Phe–Phe and the fluorinated analogue Phe(4-F)–Phe(4-F). The resulting sol–gel material was then characterised using various techniques, including probing their properties using a range of techniques, including AFM, SEM, STEM imaging and XRD. The effect of the fluorination was clear: where the silylated Phe–Phe structure gave rise to rod-shaped structures, the silylated Phe(4-F)–Phe(4-F) resulted in spherical particle formation. The use of FT-IR spectroscopy supported the presence of parallel β-sheet secondary structures and siloxane bond formation. The discussion was very much focused on the synthesis and characterisation of the silylated peptides themselves. This included the need to functionalise the peptide with the silicon, and the reasoning on the necessary formation of co-assembly by mixing the peptide within the premade sol–gel. Discussion on why such a small change in the di-peptide structures can lead to such a drastic difference in the morphological output was lively, and involved input from several members of the audience. Regarding the synthesis of this hybrid material, a comment was made on the condensation chemistry itself, and what the outcome would be if the sol–gel formation was carried out at different pH and if this could have a major effect on the formation of the sol–gel assembly (as the change in the di-peptide structure had). The solid-state NMR and Si-NMR might be used in understanding the structure (degree of bonding) of the hydrogels, *etc*.

The final talk in this session was given by Prof. Garry Laverty (Queen's University Belfast, UK), who unlike the two previous presenters, focused his contribution on peptide hydrogels for drug delivery, and the problem with the use of injectable peptides, and the impact that counterion(s) and salt formation can have on the properties of such peptide based delivery systems (**https://doi.org/10.1039/D4FD00194J**). Here, a supramolecular peptide hydrogel Napffk(CAB)y(p)G-OH, was used, and some in-depth physical and biochemical investigations were undertaken. The role of the counterion on the formulation of active pharmaceutical ingredients (APIs) was the main objective of the study. In particular, the effect of the gelation process was examined in the presence of

different acids such as HCl and trifluoroacetic acid (TFA), as well as how this would affect the scale up processes of such injectable peptides. TFA salts are often used during the solid-phase synthesis of peptides/APIs, while most APIs would be sold as their HCl salts, as well as acetate salts. Hence, the study showed that determining the biostability, cell cytotoxicity, as well as drug release in addition to rheological properties of a such peptide hydrogels formed from different salts, was an essential process to undertake. The discussion that followed was centred on "Why not use a less acidic system than TFA?". And the effect of the counterions on peptides, which has been studied, and therefore there is significant literature on, as well as the effect it has on the morphological features and rheological measurements of the hydrogel. The recent results where TFA was used within hydrogels in mice in a study from China, were discussed. The use of the $^{19}$F NMR to prove that all of the fluorine has been removed from the hydrogel was also discussed, and the reliability of that method considered. As well as how much TFA can be allowed (from a regulatory point of view) in such delivery systems. Overall, this session brought about a lively discussion on a range of issues and challenges in the use and in the application of supramolecular (hydro)gel chemistry; a subject that was revisited again later in this *Faraday Discussions* meeting.

## Session 3: Design of gelling systems

The third session of this meeting was devoted to the development of 'gelling systems' and consisted of four contribution talks: the first two contributions focusing on the use of computation and modelling in developing high throughput screening methods and means to predict fibre formations for such soft gel materials. This session was chaired by Prof. Dave Adams (Glasgow University, UK). First up was Prof. Tell Tuttle (University of Strathclyde, UK), who in his contribution (**https://doi.org/10.1039/D4FD00201F**) and presentation focused on the development of automated tools to quantify and classify self-assembly morphologies through the use of coarse-grained molecular dynamics (CGMD) simulations, employing the MARTINI 2.1 forcefield; the overall aim being to create automated tools to quantify and classify self-assembly morphologies, and to allow for reliable prediction of such assembly formations. The understanding of self-assembly pathways is of great importance for being able to predict the outcome and hence, the structure of self-assembly architectures. To achieve this, Prof. Tuttle proposed the use of five structural descriptors, that could be used

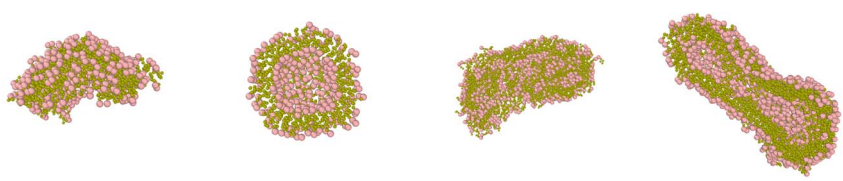


Fig. 4 Cartoon representation of four self-assembled structures formed using FF dipeptides. The backbone of these peptides is represented by the pink colour, and the side chain by the green colour. Reproduced from https://doi.org/10.1039/D4FD00201F with permission from the Royal Society of Chemistry.

when tracking self-assembly pathways. The descriptors were 'designed' to capture aggregates in transition, such as from sheets to vesicles to fibres or tubes, using an 'Aggregate Detection Index (ADI)': these being a Sheet Formation Index (SFI), Vesicle Formation Index (VFI), Tube Formation Index (TFI), and Fibre Formation Index (FFI). In demonstrating this, the system was tested with the analysis of peptide self-assembly formations, Fig. 4 (reproduced Fig. 1 from Prof. Tuttle's contribution), using a range of dipeptides. These five descriptors were shown to be a good means of capturing transitions and characterising a range of aggregates, and their morphological outcomes, which included sheets, vesicles and tubes. Such modelling can be used to facilitate high-throughput screening of dipeptide systems; this providing the platform from simulation to design of targeted nanomaterials, but Prof. Tuttle indicated that the process of carrying out such simulations was lengthy, and this analysis needs to be broken down into suitable target sizes.

The second presentation in this session was given by Dr Tomasz Piskorz (Technische Universiteit Delft, Netherlands) on predicting self-assembly formation of, in this case, the tripodal building unit based on the 1,3,5-cyclohexanetricarboxamide, Fig. 5 (reproduced Fig. 1 from Dr Piskorz's contribution, **https://doi.org/10.1039/D4FD00188E**), that results in the formation of fibril networks, from the initiation *via* aggregation, through various nucleation steps and processes, using a Markov state model of molecular dynamics simulations with 'polarizable CHARMM Drude force field', and comparing the computational prediction/outcome with experiments, involving the use of cryo-SEM imaging. The presentation by Dr Piskorz, demonstrated that each of the different processes (*c.f.* Fig. 5) could be addressed by modelling, and the mechanism of fibral and bundle formation and the structural information, deduced from the computational simulation. The processes addressed are those classically associated with the self-assembly formation of such ligands, demonstrating initial aggregate and stacking formation, which can collapse, to give rise to nuclei growth into fibres of different sizes, that grow in length through monomer absorption onto the surface of such fibres. The investigation showed that elongation and secondary nucleation processes are indeed competitive progressions. As was outlined in the presentation, the grand computational challenge is to try to

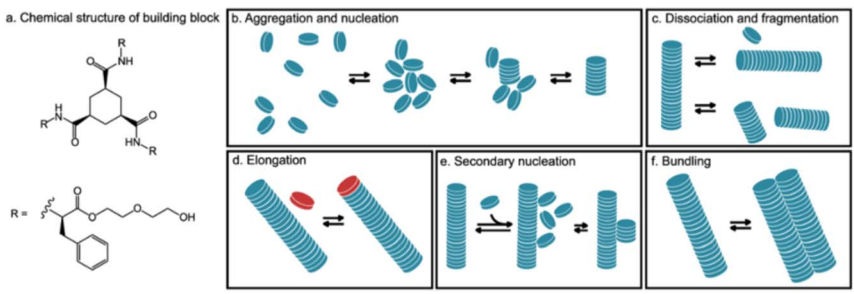


Fig. 5 The chemical structure of the 1,3,5-cyclohexanetricarboxamide used in this sturdy, and the different types of self-assembly processes and nucleation pathways studied in this contribution and presentation. Reproduced from https://doi.org/10.1039/D4FD00188E with permission from the Royal Society of Chemistry.

predict the final assembly structure and try to account for both long-range interactions as well as local interactions in the computation. The discussion and the questions from the audience that followed, was in part addressed to both speakers, and in part, centred on the capability and reliability of the use of computation to predict and shed light on self-assembly processes and the predictability of the outcome both from a structural and physical point of view (such as rheology). The question of what role the solvent plays in such processes and are the growth processes a directional motion, were raised. It should be noted that the aforementioned calculations did take solvation into account. The role of reversibility (or equilibration) and the effect of numbers of smaller fragments coming together to give large self-assembly structures, were also discussed. Finally, both speakers were asked to elaborate on how machine learning can be used to predict the outcome of self-assembly processes. The outcome of that discussion, was that it can be very challenging to build up large enough data sets to be able to have artificial intelligence (AI) or machine learning to predict the outcome of self-assembly processes; a challenge that can have a major impact on achieving the generation of selection rules to design predictable self-assembly material outcomes. An extended discussion on the simulation of different self-assembly models, *etc.* and how different shapes can be modelled took place. The ligands that can engage in 'flexible interactions', and the formation of un-ordered aggregates, that are hydrophobic and can then rearrange upon forming extended hydrogen bonding networks into ordered self-assemblies, can be modelled successfully. This discussion was then followed by a break and celebration of the 20th anniversary of the Royal Society of Chemistry journal *Soft Matter*, in some style!

The second part of this session also consisted of two presentations. These being focused on the development of antibacterial gels from small gelators and how peptide chirality can affect protein-triggered supramolecular hydrogelation, respectively. First up was Prof. Parthasarathi Dastidar (Indian Association for the Cultivation of Science, India), who gave account of his research groups work on the development of supramolecular gels from primary ammonium dicarboxylate (PAD) salts (**https://doi.org/10.1039/D4FD00154K**). The contribution and the lecture focused on the synthesis and the gelation of 20 PAD structures that were then used to gel methyl salicylate (MS) in pure water, as well as in a mixture of DMSO–water; of which *ca.* 40% were able to do so, at relatively high salt concentrations, or at 10 wt%. The objective of this gelation method was to develop drug delivery systems using the concept of 'vehicle-free drug delivery' (VFDD) where the active pharmaceutical ingredient, in this case methyl salicylate (MS), was converted into a gel through the appropriate design of a 'co-gelating' substrate, such as PAD structures, thereby avoiding the need for any secondary vehicle, and the application of this mixed gel material, Fig. 6 (reproduced Fig. 1 from Prof. Dastidar's contribution).

Some of the remaining systems gave rise to crystals that were suitable for X-ray crystal structure analysis, and the outcome of this solid-state characterisation was then used to build-up an understanding of the supramolecular interactions and the possible pathways to gelation of MS, and the formation of 1D and 2D networks. These hydrogels were characterised using both rheological measurements and imaging platforms. Also, the gels were tested for their antibacterial activity against *E. coli*.; but extensive chemical biological profiling was also

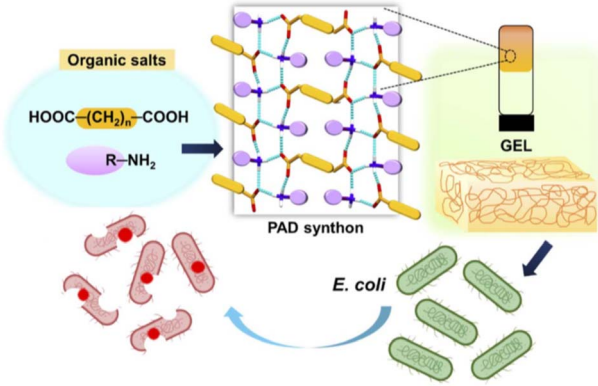


Fig. 6 The rationale behind the design and the use of organic salts in the gelation of API that can be used for vehicle-free drug delivery (VFDD); in this case for targeting bacterial infection. Reproduced from https://doi.org/10.1039/D4FD00154K with permission from the Royal Society of Chemistry.

provided in this contribution, in addition to the material and physical analysis of the VFDD systems. This lecture demonstrated how a simple self-assembly structure, and hence gels, can provide significant medicinal properties and bio-applications.

The final lecture of this session was given by Prof. Loïc Jierry (University of Strasbourg/Institut Charles Sadron CNRS, France), who presented his research on peptide chirality and how that could influence protein based supramolecular hydrogelation (**https://doi.org/10.1039/D5FD00007F**). In his lecture, Prof. Jierry attempted to answer two main questions; "How can a protein induce peptide self-assembly?" and "How can a peptide be recognized and how does it… interact with the protein?". To address this phenomenon, the group employed two heptapeptides, each possessing a dithene linker, that were formed from

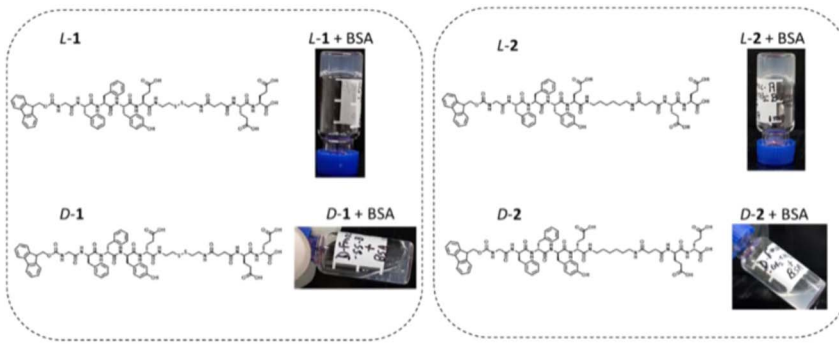


Fig. 7 The structures of the two peptide enantiomers (L and D) of L-**1** and L-**2** and D-**2**, and the pictures of their gels formed for the L-enantiomers of these peptide sequences, while the D-analogues do not give rise to such hydrogels in the presence of BSA. Reproduced from https://doi.org/10.1039/D5FD00007F with permission from the Royal Society of Chemistry.

either L or D amino acids (L-**1** L or D), that were water-soluble, Fig. 7 (reproduced Fig. 1 from Prof. Jierry's contribution). The analogues peptide L-**2** was also formed, but this structure lacks the dithene moiety, which was replaced by a covalent C–C spacer. The results showed that over time, the L-peptide in the L-**1** based structure, gives rise to viscosity changes in aqueous solution; SEM images showing the formation of nano-fibres in solution. In contrast, the L-peptide in water did not give rise to hydrogel formation. However, when the protein BSA was added to the L-peptide solution, which is stable for many months without giving rise to gelation, the formation of hydrogel was observed within minutes of the addition of BSA. In contrast, the D-peptide of L-**1** did not give rise to any viscous changes, nor did it yield a hydrogel in the presence or the absence of BSA; even upon standing for long periods of time. Gratifyingly, L-**2** did not give rise to gel formation on its own, but the addition of BSA did cause hydrogelation. The L-based L-**1** gel formation was analysed using a range of spectroscopic techniques, including the use of CD; the morphological features of this system were probed using SEM imaging, which showed the formation of nano-fibres and β-sheet organisation. While the D-analogue of L-**1** is also shown to give rise to (*via* CD measurements) interactions with the BSA, no hydrogel is formed. This phenomenon demonstrated that the two peptides must be interacting with the BSA protein in a different manner, given the striking difference in the outcome for these peptides, based on '*natural*' (L) *vs.* '*non-natural*' (D) amino acids. While the outcome is not overall surprising, given that nature would behave in similar manner, the mechanism of which these peptides interact with BSA was not obvious. Using computational modelling (molecular dynamic studies; using AMBER18) Prof. Jierry showed that the BSA can unfold the L-peptide, while this does not occur for the D-peptide. It was speculated that the former gives rise to more stability in solution, and hence, allows for stronger supramolecular interactions between the L-peptides (for both L-**1** and L-**2**), resulting in hydrogel formation. Furthermore, other proteins, such as alkaline phosphatase and carbonic anhydrase both showed the same trend as seen for BSA for these L/D-peptides. In contrast, the use of the protein's urease or β-galactosidase did not result in such protein triggered gelation. However, in all cases, these proteins always resulted in the formation of nano-fibril networks for the L-peptides in solution. Hence, the overall results demonstrated how chirality, and the nature of the protein employed, can play a major role in directing self-assembly formation and the generation of gellated material. But this had indeed been proposed/highlighted in the Spiers Memorial Lecture delivered by Prof. Pochan, in the self-assembly process and in enabling the hydrogelation to take place.

The discussion that followed these two presentations was very lively. Prof. Dastidar was asked about the selectivity of the antibacterial effect and in which environment it can be employed; such as against biofilms, and if there was a correlation between the supramolecular structure and the antibacterial effect. An energetic discussion on the crystal packing, and how it can be used to deduce the supramolecular interactions in the gelation phase, took place. Interesting related discussion also took place around the possibility to manage the formation of crystals from less competitive solvents that would mimic the gellated samples in a closer manner. Hence, the outcome from this discussion… "*can we learn from the solid-state information what the self-assembly will 'look like' in more competitive media*" and "*how much can one learn from the crystal packing of one system to employ*

*that as a model for understating gelation properties of structurally related systems*", was discussed and debated at length.

In line with some of the discussion taking place in previous sections, the importance of sample preparation and reproducibility was also eagerly discussed. Prof. Jierry was probed on if he had titrated one of the peptides into the other and varied the concentration of BSA and *vice versa*. Also, a discussion on if the binding of the peptide is non-specific with BSA, given that other peptides resulted in gelation and that the interaction is highly dynamic – as had been pointed out by the two earlier presenters in this session – and if the peptide–protein interaction gives rise initially to the formation of globular systems. It was concluded that the use of D/L hybrids would be interesting to investigate with BSA and see if the understanding of the gelation pathway might be deduced from that. After this discussion the formal proceedings of the second day of the *Faraday Discussions* ended, being followed by the conference dinner.

## Session 4: Multicomponent systems

The final session of this *Faraday Discussions* meeting was chaired by Prof. Krishna K. Damodaran (University of Iceland, Iceland) and focused on the formation and study of multicomponent supramolecular gels. In part, this was a direct continuation of the previous session where the use of small (low molecular weight) organic gelator molecules were discussed within more complex systems and within a range of applications. This session consisted of five presentations. First up was Prof. Emily Draper (University of Glasgow, UK), who presented her work on the development of low molecular weight gelators (LMWGs) based on pyrelinediamide Fig. 8 (reproduced Fig. 1 from Prof. Draper's contribution, **https://doi.org/10.1039/D4FD00185K**) that the Draper group has been studying for some time, and how it can be employed within a polymeric blend to achieve 3D printed materials; the rheology of which can be probed, before, during and after printing. Small-angle neutron scattering was also used to provide insight into the process of 3D printing. This presentation addressed an important issue within the application of supramolecular gels. Many LMWGs have been studied to date, but their application in hydrogels or organogels has been in general, less so. One of the reasons for this is the problem associated with preparing printable samples of LMWGs based gels, an issue that a lot of researchers are having, and an experience which the author of this concluding remarks knows only too well(!),[16] as the gel printing can be affected by kinetics, viscoelasticity and thixotropy of the gel. Indeed, as Prof. Draper pointed out in her contribution, *'most*

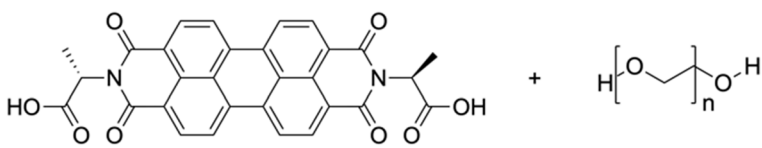


Fig. 8 The LMWG amino acid derived pyrelinediamide **PBI-A**, and the polymer PEO used in this study by the Draper group. Reproduced from https://doi.org/10.1039/D4FD00185K with permission from the Royal Society of Chemistry.

*reported examples of hydrogels suitable for printing have been discovered through serendipity'* and have not been achieved by design. Moreover, many gels formed from LMWGs are soft and ill-prepared for use in 3D printing, and it can be difficult to characterise the rheological properties and the changes that such gels go through *via*, or during, the printing process. Hence, the undersigning of the changes that the supramolecular gel can undergo during printing is limited, and being able to resolve this drawback in general was one of the main objectives of this study, as eluded to above. With this in mind, Prof. Draper and co-workers, prepared gels based on **PBI-A** alone, as well as within a polymer, using the non-gelling polymer additive **PEO** (Fig. 8), that was added to create the **PBI-A**/polymer blend. The importance of employing both types of systems (*e.g.* supramolecular as well as covalent polymers), within the same sample had already been highlighted at the beginning of this *Faraday Discussions* meeting, where its application was referred to as the *"best of both worlds"* and indeed its importance was demonstrated herein. Using a range of physical characterisations demonstrated that indeed the printing of the **PBI-A** formulated LMWG did have a major effect on the resulting printed gel; this investigation included the use of RheoSANS (simultaneous rheology and small-angle neutron scattering) during the printing process. *The author concluding that rheology alone cannot give detailed enough information on the state of the gel during the printing, while RheoSANS can*. Given the nature and the importance of the topic of this contribution, the discussion that followed, touched on a range of issues, such as: how does the printing head influence the physical parameters of the gel (when not using syringe, or extrusion-based printing)? In fact, the discussion concluded that indeed, '*everything affects the printing*' and for successful printing it… needs to hit that '*sweet spot*'! Also, discussion on the weight of the gel, and how this can be a problem during the printing process was raised. And that the properties of the gel (that is being printed!) is affected, for instance, upon printing a layer of gel on top of another layer of gel (already printed). This is particularly relevant in the printing of biomimetic material. One of the key findings from this investigation was that the raw material employed does not produce the same properties upon sheering (the flow is very different, as even seen in the morphology investigation) before and after printing. This also connected with the issue of how a printed hydrogel ages over time! And is there a problem associated with morphological changes taking place, that are associated with the printing process. Further discussion took place on this research, highlighting a clear indication of the importance to gain deeper understanding into the printing process of such multicomponent supramolecular gels, particularly during the printing process, or *in situ* formation itself.

The next lecture in this session was also concerned with the use of LMWGs gels, these being based on short peptides. The contribution and lecture were given by Prof. Bradley Nilsson (University of Rochester, USA), who presented his work on the use of three cationic fluorenylmethoxycarbonyl phenylalanine based LMWGs (two of these possessing three and five fluorine atoms on the phen ring), namely Fmoc-Phe-DAP, that forms hydrogels upon addition of anionic forms of amino acids such as aspartate and glutamate (**https://doi.org/10.1039/D4FD00198B**). These systems were shown to form hydrogels upon mixing, however only Fmoc-3F-Phe-DAP upon blending with glutamate formed a stable (or self-supporting) hydrogel; the remaining two LMWGs only resulted in gels that

were (mechanically) 'weak'. And, in the case of aspartate, none of the resulting gels were shown to be self-supporting. This alone, clearly demonstrates the importance of the number of fluorines on the phen ring in the self-assembly process. These gels were also formed in different molar ratios of the two organic ions, to investigate how stoichiometry could influence the hydrogelation process. The addition of NaCl was also investigated. The gels formed using Fmoc-3F-Phe-DAP, were characterised using conventional methods, their rheological properties examined, as well as their morphological nature probed using TEM imaging. This latter investigation showing that the nature of the anion and the stichometry played a major part in the self-assembly process and in the concomitant materials outcome.

The discussion that followed focused on a range of issues and possibilities, such as the nature of the fluorinated phen ring, its role in the hydrogelation process, and in-fact, what makes them unique! Why did the use of Fmoc-5F-Phe-DAP not result in the formation of strong gels while Fmoc-3F-Phe-DAP does? The discussion revealed that Prof. Nilsson had made several other analogues of these systems, and some of these would crystallise rather than form a soft-material; this discussion became of a similar nature to that above, where the crystal structures of cationic gelators was used to deduce information on the nature of the self-assembly formation in the gel-state. The effect of the salt and its importance was further discussed together with possible cross-linking of the amino acid side chains; and if flexibility played a role in the gelation process. As for many discussions highlighted here, the 'predictability' of the outcome and if one could elucidate the structure/outcome for such multicomponent systems was also debated. Intense discussion on the characterisation and the use of scattering techniques, referring to some of the other talks as well, was very informative.

The last lecture of this opening morning session of the final day of the *Faraday Discussions* meeting, was given by Prof. Bart Jan Ravoo (University of Münster, Germany), focusing on the development of multicomponent gels, consisting of a photoresponsive LMWG peptide (AAP-FGDS) as a supramolecular hydrogel (possessing an arylazopyrazole derivative to allow for effective photo-isomerisation) and non-photoresponsive covalent agarose gel (polymer). This system was doped with NIR emitting (containing lanthanide ions) nanoparticles, the emission of which could be generated through two phonon excitations leading to the photoisomerization of the AAP-FGDS gelator resulting in a softer gel. The rational for this mixed supramolecular/polymer system being seen in a schematic form in Fig. 9 (reproduced Fig. 1 from Prof. Ravoo's contribution,**https://doi.org/10.1039/D4FD00203B**) and the proposed system has potential for *in vivo* applications. The work presented by Prof. Ravoo demonstrated the versatility that multicomponent gel systems have to offer in the formation of supramolecular responsive materials. Having examined the general material and morphological properties of the gel, Prof. Ravoo demonstrated the use of the photo-isomerisation, which allowed for phase change from a gel structure to liquid form upon irradiation of 980 nm light, which switches from the *E*-isomer to the *Z*-isomer under NIR irradiation, and that the subsequent irradiation using 520 nm light reversed this phase transition, due to $Z \rightarrow E$ isomerisation. This gave rise to hydrogel formation that possessed the same material properties as the 'initial' self-supporting gel; the use of UV-vis absorption spectroscopy allowing for the monitoring of the isomerisation process, which

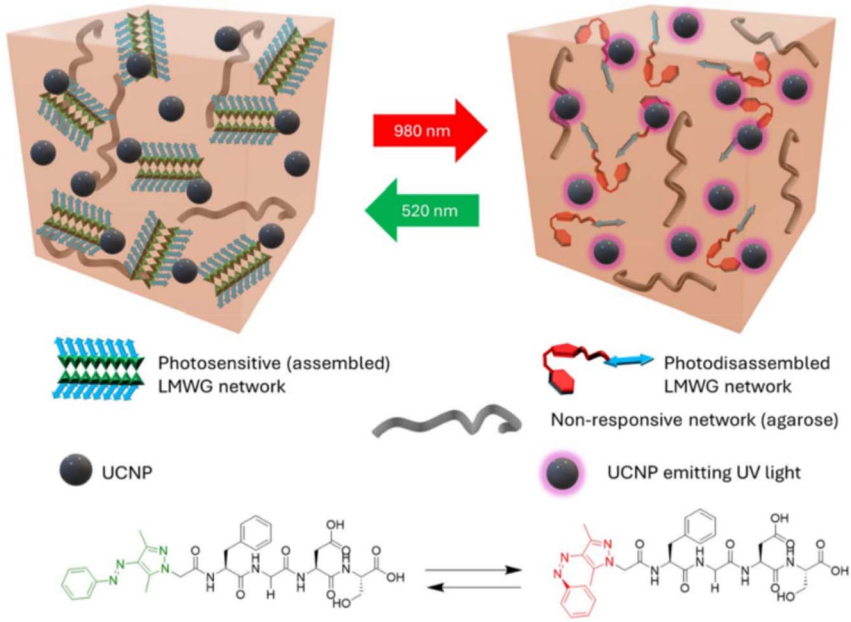


Fig. 9 Schematic representation of the 'three' component hydrogel consisting of the peptide based light responsive LMWG, possessing arylazopyrazole moiety, agarose gel (non-photoresponsive component) and upconversion nanoparticles enabling for generation of NIR light. Reproduced from https://doi.org/10.1039/D4FD00203B with permission from the Royal Society of Chemistry.

facilitated this phase transformation. Even though the process was slow, such photo-driven changes open's up a range of applications for such multicomponent supramolecular gel systems. The phase transformation was also probed using rheological measurements, which demonstrated the NIR irradiation resulted in the gel becoming significantly softer with some loss of its elastic properties. The key here was the structural nature of the azo-switch, the arylazopyrazole, which Prof. Ravoo has worked on for several years, as it facilitates the 'switching' between the two states (*E* and *Z*) with high efficiency, and not partially as is often the case with the more traditional azobenzene based systems. The morphology of the hydrogel was examined using SEM and TEM imaging, where the presence of the nanoparticles was confirmed within the polymeric matrix. Furthermore, the doped upconversion nanoparticles gave rise to lanthanide centred emission upon excitation of the peptide sensitiser. The discussion touched down on many aspects of the lecture and in particular, on the potential of incorporated additives or drug candidates, into the switchable gels that can then be delivered upon photoexcitation. Prof. Ravoo indicated that such endeavours had been in part undertaken using analogues systems, but not for the system presented here. The issue is of potential reabsorption of the light energy with the gels but this can be overcome using different particles. This system provides a platform for a range of applications, and some of these were discussed in some detail.

The next lecture in this session was given by Prof. Silvia Marchesan (University of Trieste, Italy), who focused on the use of nano-IR, as well as other techniques to

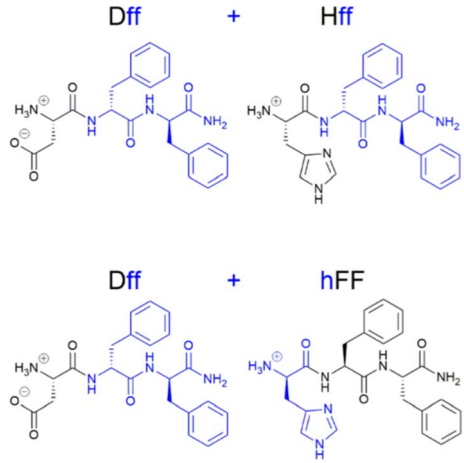


Fig. 10 The structure of the tripeptides employed in this study and the two combinations employed. Reproduced from https://doi.org/10.1039/D4FD00193A with permission from the Royal Society of Chemistry.

probe tripeptide co-self-assembly formations; the question asked being 'is it possible to identify if such peptides, as heterochiral tripeptides, co-assembled or self-sort' during the self-assembly process to give hydrogels. The tripeptides employed here being based on the use of Phe–Phe with terminal His and Asp units, Fig. 10 (reproduced Scheme 1 from Prof. Marchesan's contribution,**https://doi.org/10.1039/D4FD00193A**). The self-assembly of the peptides themselves and their mixtures were triggered by pH at two different concentrations: 10 and 25 mM. Both yield gels, and they were shown to possess thermo reversibility while all the hydrogels formed in this work showed self-healing properties. Morphological investigations into the gels, using TEM imaging, showed them to be formed from dense nanofibrillar networks. The use of nano-IR and other measurements demonstrated that these gels were successfully co-assembled, and that self-sorting did not occur, providing useful insight into the packing modes of the peptides, suggesting amyloid-like fibres were formed in all the two peptide component systems (*c.f.* Fig. 10). The discussion that followed, centred on the sample preparations, the physical analysis and the use of nano-IR. As in many of the earlier discussions, the issue of reproducibility was discussed together with the sample preparation, and how structure affects the mechanical outcome and properties of the gels.

The final lecture of the scientific programme of this *Faraday Discussions* meeting was given by Prof. Huaimin Wang (Westlake University, China). Related to the topic of the previous lecture, Prof. Wang focused his contribution and lecture on a study that systematically explores how hydrophobic amino acid linkers can impact the morphological nature within two-component co-assembly systems that have strong electrostatic interactions (**https://doi.org/10.1039/D4FD00209A**). The objective here was to attempt to generate programmable peptide-based hydrogels with predictable morphological and mechanical outcomes. The investigation here was based on previous work, consisting of the peptide scaffolds Ac-FKFK-$NH_2$ and Ac-FEFE-$NH_2$, with side-chain structures –

GG, AA, LL, VV, and NleNle – as linkers, being incorporated into this design that possessed varying hydrophobicity. Using a range of physical and imaging characterisation studies (of the same nature as discussed for several of the above contributions), the results showed that the nature of the hydrophobic linker influenced both the assembly behaviours and the structural properties of the resulting supramolecular gels. These gels were assembled at different rates; some being formed within a few hours while others took days to form in water at neutral pH. Apart from NleNle which did not give rise to a gelled material, and only precipitation was observed over time. The rheological properties of these gels were studied, as was other material properties, which include the use of AFM imaging. This gave additional insight into the mechanical properties of the gels. TEM characterisation of both the single peptides and mixed systems (of the positively and negatively charged peptides), showed that the morphology varied within these samples as shown in Fig. 11 (reproduced Fig. 5 from Prof. Wang's contribution). The formation of two-dimensional nanostrip structures, with β-sheetlike arrangement, was taken as proof of the critical role of the hydrophobic interactions within these systems. The latter helping in the generation of stable assemblies. As was the case in previous sessions, the final discussion section of this meeting, involved the lively exchange of opinions and suggestions, where some of the topics previously mentioned resurfaced. As before, the discussion highlighted the unique nature of the *Faraday Discussions* meeting format and was focused on the sample preparation, the use of different characterisation techniques, and reproducibility, highlighting many of the topics discussed throughout the three-day meeting. The underlying objective of the last two lectures of this meeting, was to achieve control over self-assembly pathways in the

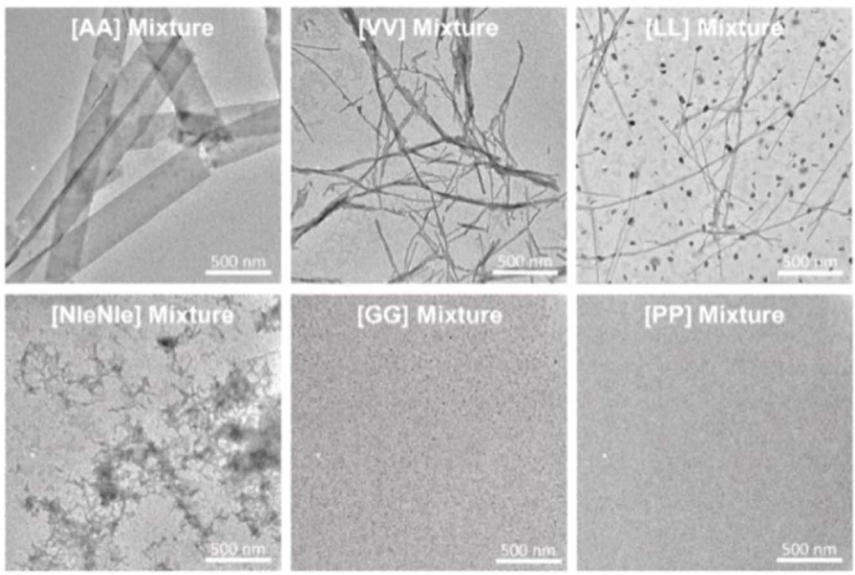


Fig. 11 TEM images of different di-peptide based hydrogels formed (from the two-component systems) at pH 7.4. Reproduced from https://doi.org/10.1039/D4FD00209A with permission from the Royal Society of Chemistry.

formation of peptide-based hydrogels. To achieve that, examples of gelators must be designed, synthesised and characterised in detail. The use of scattering techniques is an important means of achieving analysis of the nano-assemblies, as indeed was highlighted in several of the lectures in the last session of this *Faraday Discussions* meeting.



## Conclusion

This meeting on supramolecular gels was a fantastic opportunity for reviewing the current state of the art, looking towards the future, and discussing the many possibilities that soft matter chemistry has to offer in a range of applications and through interdisciplinary work. A significant part of the presentations during this meeting were devoted to the use of peptide-based structures, and the range of techniques and means to characterise hydrogels and their assembly pathways. At the same time, the role that LMWGs have and their elegance in the formation of multicomponent gels, and in printable materials, *etc*. was also demonstrated. Despite the rich number of results presented and discussed, I could not help feeling that as a subject, we still have a limited understanding of how to control the various self-assembly pathways that lead to formation of supramolecular gels. How and why minor structural changes, such as the order of the amino acids within a peptide or their chirality nature, their charge, hydrophobic and lipophilic nature, can have a major impact on the morphological outcome of such materials, remains a challenge to elucidate and predict accurately, and in a reproducible manner. We saw however, that with improved instrumentation, better imaging techniques, with high resolution and accuracy, and access to a range of new and less explored imaging platforms and scattering techniques, we are rapidly gaining better understanding of such phenomenon. It was discussed that electron microscopy of dried samples, small-angle scattering and spectroscopy, currently dominating the characterisation of gels, are unable to provide understanding of the complete structural arrangement of molecules within gels, and this therefore prevents our understanding of targeted modification of the gelator molecules. However, it should be emphasised that the cryo-EM technique widely used in structural biology has great potential for obtaining high resolution imaging of original (not dry) gel samples. Although there are still challenges, this technique provides very high promise for revealing the mechanism of assembly and gelation and will play a transformative role in understanding the atomic structure within gels and therefore allow for its rational design with targeted properties. On the other hand, technology, and improved computational power and larger data sets, greatly aid us in diving deeper into the understanding of what mechanisms are at play, and enabling us to begin to gain real control over self-assembly processes to a degree. I believe that the advent of faster computing, machine learning and the use of AI will without any doubt be a gamechanger in accelerating our understanding and confidence in achieving this.

There were many exciting talks presented within the three days we had in sunny Glasgow this spring; some focused on how structure relates to function, others on their biomaterial properties, compatibility, physical properties and of course, their applications! How to apply gels in printing, the formation of multicomponent systems, their applications, in medicine/or as new coating materials, *etc*. The combination of supramolecular gels and more classical

polymeric systems is a combination that can greatly help in ensuring gel robustness and mechanical properties (*the best of both worlds!*). At the same time, the use of photo-switches within such gel matrixes, can allow for control over mechanical output; a beautiful example of that was Prof. Ravoo's '*phase (or shape) shifting*' tri-component gel system. This *Faraday Discussions* was an excellent meeting! I walked away extremely excited about the prospects of supramolecular gels in the future, and the types, complexity and applications that they have to offer in so many areas of research! I look forward to the next time we meet up and celebrate progress in another *Faraday Discussions* meeting. I would finally like to thank the Royal Society of Chemistry, the co-Chairs, and the organising committee for delivering such a great *Faraday Discussions* meeting.

## Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

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