# Equilibrium gels of limited valence colloids

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## ARTICLE INFO

## ABSTRACT

Gels are low-packing arrested states of matter which are able to support stress. On cooling, limited valence colloidal particles form open networks stabilized by the progressive increase of the interparticle bond lifetime. These gels, named *equilibrium gels*, are the focus of this review article. Differently from other types of colloidal gels, equilibrium gels do not require an underlying phase separation to form. Oppositely, they form in a region of densities deprived of thermodynamic instabilities. Limited valence equilibrium gels neither coarsen nor age with time.

## 1. Introduction

Gels are ubiquitous in nature. At the atomic and molecular level, network liquids form extended open transient networks of bonds of quantum-mechanics origin (tetrahedral in water and silica) [1,2,3•]. In the amorphous state, the bonding pattern is frozen in a permanent structure. At polymer level, gels arise from multiple chemical or physical connections between distinct chains [4,5]. At colloidal level, gels occur when the inter-particle interaction strength becomes considerably larger than the thermal energy $k_B T$ and particles stick together forming a disordered highly porous material.

The origin of the colloidal gel state is one of the fascinating questions in soft matter [6••]: why particles prefer to form an arrested state of matter (a disordered solid), despite the very limited amount of occupied volume, i.e. in the absence of excluded volume caging effects? Does colloidal gelation always require an underlying phase-separation? When and how the gel state is a real equilibrium state of matter, that does not age or coarsen with time? Some of these questions are discussed in this article.

We specifically focus on particle colloidal gels [6••,7,8], e.g. on systems in which the monomeric unit is a particle, although some of the concepts we will develop are also relevant to molecular and polymeric gels. While we deliberately discuss only one-component gels, the same ideas can be generalized to multicomponent systems [9•,10]. We thus concentrate on systems in which gelation arises from the onset of a network of long-lived interparticle bonds between identical particles. The solvent, when present, and its quality only enters in the definition of the effective interaction potential between particles.

In analogy with chemical gels (e.g. systems with permanent bonds), colloidal gelation has often been identified with percolation, e.g. with the spontaneous formation of an infinite spanning cluster that provides rigidity to the material. However, very often, at the percolation locus (a line in the temperature-density plane), the lifetime of the inter-particle bonds is very short and no dynamical signatures of arrest are detected in experimental observables. Under these conditions, the incipient spanning cluster is transient and it restructures itself on the same timescale of the bond lifetime. Gelation in these systems thus requires temperatures significantly smaller than the $T$ at which percolation is encountered. As a result, kinetic arrest in a disordered solid-like structure is commonly observed when $T$ is much smaller than the inter-particle attraction strength, e.g. in the same $T$-window where phase separation takes place. Notable exceptions, discussed below, are provided by systems in which the bond lifetime is decoupled from the thermodynamics of the system, as in systems in which strong activation barriers separate bonded and non-bonded states [11,12].

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The most common colloidal gels (depletion gels [13•,14]) are formed by a quench into a thermodynamic unstable region, followed by spinodal decomposition and kinetic arrest, which finally prevent a complete phase-separation [15,16]. This process creates dynamically arrested structures encoding information of the underlying decomposition process in the resulting material [6••,17,18]. Such gels are in a non-equilibrium state and display restructuring processes aiming at slowly completing phase-separation. In the case of extremely deep quenches, the phase separation becomes equivalent to an irreversible aggregation process, commonly indicated as diffusion limited cluster aggregation (DLCA). Under these conditions, fractal aggregates grow, progressively filling up space until a macroscopic structure forms. As shown in several experiments [15,19•,20] and theoretical studies [21], the structure of DLCA gels displays the hallmark of spinodal decomposition, e.g. a coarsening peak in the static structure factor at low wavevectors.

Another type of colloidal gels originates from the competition between short-range attraction (often of depletion origin) and long range repulsion (often of electrostatic origin). Such competition suppresses phase separation in favour of the formation of finite size aggregates (microphase separation). Depending on the actual shape of the inter particle potential, these clusters can be highly anisotropic and give rise to slowly aging filamentous gels [22•,23].

In the last decade, the concept of equilibrium colloidal gels, i.e. gels that do not age and display a remarkable thermodynamic stability, has been developed in a series of studies primarily aiming at understanding the phase behavior of limited-valence patchy colloidal particles [24•,25••,26,27,28•,29], establishing a strong connection between the limited valence at particle level and the formation of an equilibrium gel as a collective state. These new colloids are characterised by highly anisotropic interactions, mimicking bonding in network liquids [3•,30]. In colloids interacting via isotropic attractive forces [31–34] (as for the depletion interaction [35]) the condensed phase (the analog of the liquid phase in atoms) is typically constituted by a dense local structure. Indeed, to minimize the system energy, particles are surrounded by the geometrically controlled maximum number ($\approx 12$) of neighbours. If such particles are brought to a temperature significantly smaller than the attraction energy scale (or equivalently if the attraction strength is significantly larger than thermal energy at ambient temperature), particles will cluster into aggregates, eventually separating into a dilute gas of monomers and a dense liquid. When the colloidal particles interact via a limited number of bonds (or valence $f$) the lowest energy state is achieved when all possible bonds are formed. But now the number of bonded neighbours is fixed by valence. The resulting *empty* liquid [25••] is characterised by a density that is approximately reduced by a factor $f/12$ with respect to the isotropic case. If a system of limited-valence patchy colloids is then brought to a temperature significantly smaller than the attraction energy scale, particles will cluster into open aggregates. Only at low densities, it will eventually separate into a gas of monomers and an *empty* liquid, the structure of which can be envisioned as an open network of bonded particles. For tetrahedral patchy colloids, the typical volume fraction occupied by particles in the empty liquid state is approximately 25–30 %, as compared to the $\approx 60\%$ packing in simple liquids.

What we are learning from these considerations is that limited valence is a fundamental requisite to generate open stable equilibrium phases at low *T*. A schematic representation of the phase-diagram of low-valence particles in shown in Fig. 1. Thus a window opens up in the density region between the gas-liquid coexistence and the glass (where excluded volume dominates) in which the liquid state remains stable. Upon cooling the system inside this density region, particles becomes progressively connected by physical bonds, until the system reaches its lowest energy state, in which all possible bonds are formed. Further cooling does not change any longer the structural properties of the gel, affecting only the time-scale of
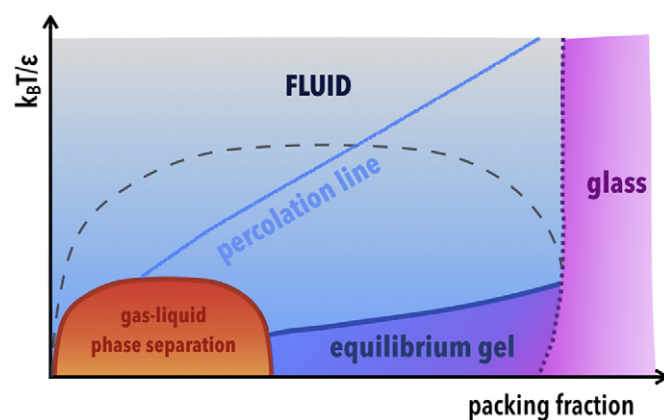


**Fig. 1.** Schematic phase diagram of limited valence particles, particles interacting via the excluded volume repulsive interaction complemented by a small number of attractive sites (patches). Compared to the corresponding isotropic case (e.g. same depth and same range of the attractive potential), the gas-liquid phase separation is only present in a limited region of densities (full line: limited-valence case, dashed line: isotropic case). The critical temperature is also significantly reduced compared to the corresponding isotropic case. Between the phase-separation region and the high density glass region, a window of intermediate densities exists in which the system can be brought at very low temperatures in a homogeneous state. As for the glass case, in which arrest is driven by caging induced by excluded volume interactions, the arrest line in this intermediate density region can be empirically defined as the line at which the relaxation time of the system (slaved by the bond lifetime) becomes comparable to the experimental time scale. Below such line the system becomes arrested, forming an equilibrium gel. Note that equilibrium gels cannot be formed when particles interact via standard (core repulsion plus attraction) isotropic potentials, since in this case the gas-liquid coexistence curve extends up to the glass region. The percolation locus, defined as the locus at which an incipient spanning cluster of bonded particles first appears, is always located at *T* higher than the gas-liquid critical temperature. Commonly, the bond lifetime at the percolation locus is much smaller than macroscopic observation times. Thus, even well below percolation, the system retains its fluid state. In very rare cases in which the bond lifetime is comparable or larger then the macroscopic observation time at the percolation locus, then gelation coincides with percolation.

bond breaking and reforming. In the most simple conditions, such dynamics is controlled by the energy scale of the bond and follows an Arrhenius law. When the lifetime of the bonds becomes longer than the experimental time-scale, the network structure does not change during the observation time and the system behaves as a gel.

In summary, equilibrium gels do not require an underlying phase separation. They form at low *T* in a intermediate density window which exists only when particles primarily interact via a limited number of directional interactions. The empty liquids progressively transform in equilibrium gels with the increase of the inter-particle bond lifetime on cooling. Equilibrium gels are thus non-aging percolated networks at a low particle packing fraction, whose value is controlled by the valence. When the average *f* approaches two (for example by mixing together bi- and three-functional colloids), the system forms very long chains of bi-functional particles with branching points provided by the multi-functional particles, resulting in a very empty network [9•,25••,26,36].

## 2. Experiments on limited valence colloids and equilibrium gels

In the last years a significant effort has gone in the direction of synthesizing colloidal particles with anisotropic interactions [37••,38]. Beyond Janus colloids [39,40], particles whose surface is divided in two part with different physico-chemical properties, particles with multiple patches are becoming progressively more available [41–50,51•,52]. The possibility to modify the patch-patch interaction acting for example on the hydrophobicity of the surface or by binding on the patch surface specific chemical species (often
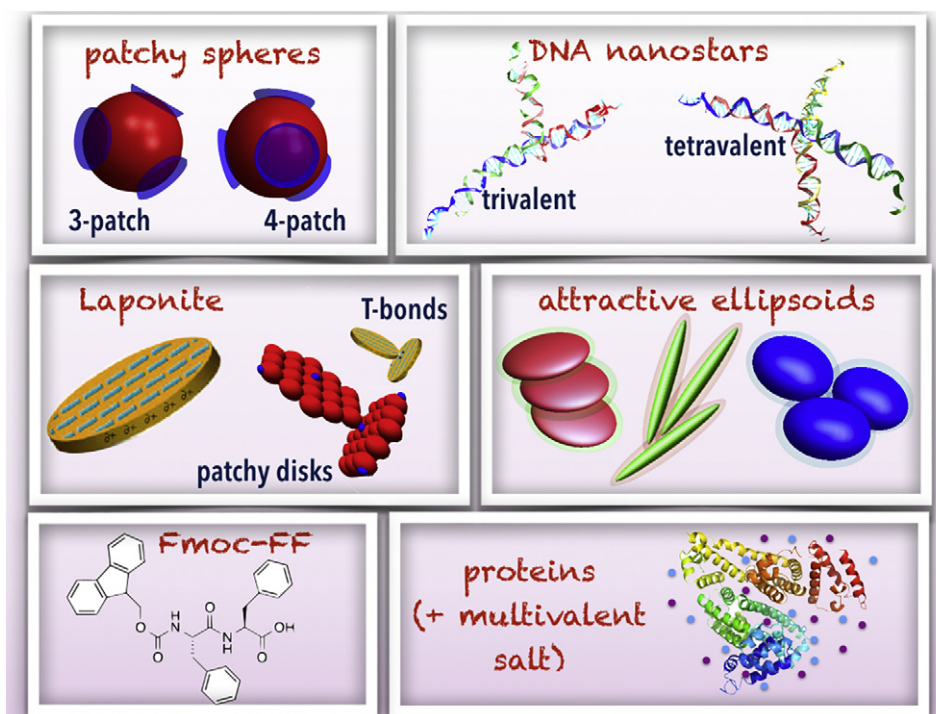
**Fig. 2.** Illustration of several model systems, both theoretical and experimental, discussed in this article. In order, a patchy particle model [53], the DNA-nanostars, the laponite discotic platelet [54], oblate and prolate attractive ellipsoids [55], the Fmoc-FF molecule [56] and a protein in the presence of multivalent salt providing limited interactions [57].

a DNA sequence to capitalize on the bonding selectivity) opens the way to a very large number of future applications and experimental realizations of equilibrium colloidal gels. Fig. 2 shows a cartoon of the model systems which have been so-far investigated to highlight the equilibrium gel behavior, discussed in the following sections.

### 2.1. Laponite

The first experimental evidence of a phase-coexistence limited to very small densities, contiguous to a gel state [58••] has been provided by a study of Laponite, an industrial synthetic clay that, dispersed in water, forms a suspension of nanometre-sized discotic platelets with inhomogeneous charge distribution and directional interactions [54] (Fig. 2). It has been suggested that the opposite sign of the charges on the rim and on the face of each platelet favours the formation of T-configurations in which the rim of one platelet sticks to the face of a neighbour one. The limited number of such T-configurations is responsible for the limited number of contacts (valence). The strength of this electrostatic bond is significantly larger than the thermal energy, de facto giving rise to an irreversible kinetics in which bonds are progressively formed. Experiments show that for concentration smaller than 1 wt% the samples undergo an extremely slow phase-separation process into a clay-rich (gel) and a clay-poor (fluid) phase. This very slow phase separation process involves a transient in which the system, which forms a fluid solution when prepared, becomes progressively solid-like before the final macroscopic separation takes place. Independently from the starting concentration (but smaller than 1 wt%) the final concentration of the clay-rich phase is always 1 wt%. Samples prepared with concentration larger than 1 wt% remain in a homogeneous state at all times. X-rays scattering experiments [58••] confirmed that for $c < 1$ wt% the scattering intensity progressively increases with waiting time, a signature of a very slow ongoing phase-separation, while for $c > 1$ wt% it approaches a time-independent value, an expected signature of an equilibrium gel. Similar conclusions have resulted from the experimental investigation of other clays, including high aspect ratio Montmorillonite [59].

In all cases, a region of thermodynamic instability has been detected at low densities, consistent with the theoretical expectation by invoking an effective (although unknown) limited valence of the clay particles. It is interesting to note that in Laponite the progressive increase in the number of bonds is driven by an irreversible aggregation process. In this respect, it could appear odd that Laponite gels have been considered as an example of equilibrium gels. This association has been supported by theoretical work [8,60,61] demonstrating that systems of limited valence particles — when rapidly brought to very small temperatures to simulate an irreversible aggregation process — evolve in time by progressively decreasing their effective temperature. Such a mapping between aging time and temperature (in equilibrium) has been invoked to interpret Laponite phase behavior in the context of limited-valence equilibrium phase diagram [58••].

### 2.2. DNA-nanostars: phase diagram and equilibrium gels

A definitive experimental proof of the effect of the valence on the phase-behavior requires the ability to synthesize bulk quantities of particles with different valence but identical bond interactions. This has been achieved capitalizing on recent developments in DNA nanotechnology, i.e. on the idea that a proper selection of DNA strands can result into the self-assembly of constructs with well-defined shape. Among these, DNA nanostars with a central flexible core of unpaired basis and a variable number of double helix arms have been realized (see Fig. 2). The DNA nanostars self-assemble, starting from a solution of properly selected isolated single strands at 90 C, when slowly cooled below $T_{assembly} \approx 60$ C (a value slightly depending on the solution salt concentration), with a high yield. Below $T_{assembly}$, these constructs constitute stable ideal patchy colloidal particles with well defined number of patches (the number of arms) and well defined interaction strength (controlled by a six-base long self-complementary sequence at the end of each arm). The $T$-dependence that characterises DNA hybridization of the six-base binding sequence offers the opportunity to investigate the limited $T$-interval between $T_{assembly}$ and $T = 0$ C, from the case of complete

absence of inter-nanostar bonds to the fully bonded limit, i.e. the entire phase behavior.

The phase diagram of tetravalent and trivalent DNA nanostars (Fig. 2) has been experimentally investigated in Ref. [62••]. For both valences, a clear phase-separation region has been observed, with the critical $T$, the critical density and the density of the coexisting dense phase $\rho_l$ all decreasing on going from valence four to valence three, in full agreement with theoretical predictions [63].

The multi-valent DNA nanostars form equilibrium gels. Indeed for $\rho > \rho_l$ the system does not encounter phase-separation upon cooling, and it remains homogeneous for all $T$. On cooling, different nanostars progressively bind to form a network where all possible bonds are formed (see Fig. 3). The correlation function of the density fluctuations, measured via dynamic light-scattering (DLS) experiments [30,62••,64], shows a progressive increase both of the relaxation time $\tau_\alpha$ and of the relaxation amplitude on cooling. This is shown in Fig. 4. The same figure also reports for comparison the density autocorrelation function for one of the limited valence models previously investigated theoretically [24•]. The increasing amplitude of the relaxation process on cooling is a signature of the progressive growth of the network. In the DNA-nanostar system, the relaxation time increases by more than four orders of magnitude before exceeding the experimental accessible time window, a clear indication of the formation of an arrested state of matter on the experimental time scale. The $T$-dependence of $\tau_\alpha$ is well described by an Arrhenius law, with an activation energy proportional to the binding free-energy of the sticky sequence, suggesting that the decay of the density correlation is slaved to the elementary bond-breaking process. It has also been reported that $\tau_\alpha$ does not show a detectable wave-vector dependence, an uncommon behavior for a particle gel [30]. An Arrhenius law also characterises strong network-forming liquids, suggesting that equilibrium gels are indeed the colloidal analog of these atomic and molecular systems.

The DNA nanostar gel is clearly a very good candidate for experimentally testing the properties of equilibrium gels. The viscoelastic properties of this class of materials will possibly be the focus of future investigation. Preliminary results suggesting that the viscosity also follows an Arrhenius law [30]. The temperature and frequency

dependence characterising the viscosity in equilibrium gels will hopefully be also investigated soon.

### 2.3. Reentrant equilibrium gels: a system with T-dependent valence

The ideas previously discussed are not only useful to interpret the phase behavior and the dynamics of particles with a fixed number of attractively interacting patches. They also apply to colloids with a $T$-dependent valence, as telechelic star polymers [66] or colloids interacting with dominant dipolar or quadrupolar potentials. In the last case the small valence builds up progressively on cooling due to the preferential sampling of the two or four directions in which the interaction potential has a minimum. A typical example is provided by ferrofluids, i.e. colloidal solutions of particles with a net electric or magnetic dipole, promoting at low $T$ the formation of long polymer-like self-assembled rings and chains of particles. For larger $T$, branching points of different type [67], effectively provide connections between different chains and rings. The decrease in the number of branching points on cooling is effectively equivalent to a reduction of the average valence of the system, which is accompanied by a progressive decrease of the density of the coexisting liquid. One can thus expect that in dipolar systems, the gas-liquid phase separation, if present, shows a pinched shape, in which the density of the coexisting liquid progressively approaches the density of the coexisting gas on cooling. This idea, first proposed by Tlusty and Safran for dipolar hard spheres [68•], has indeed been realized in a model of particles with dissimilar patches promoting respectively chaining and branching [69,70]. A pinched Safran-like phase diagram has also been observed in a simulation of a binary mixture of tetravalent and monovalent particles with competing bonding [71,72]. Very recently, such a thermodynamic scenario has been reproduced experimentally with tetravalent and monovalent DNA nanoconstructs, encoding in the sequence of the DNA strands the physics of the competing bonding [73]. On cooling, the system first assembles into a strong network formed by the association of the tetravalent particles. On further cooling, the monovalent particles preferentially start to bind to the tetramers, melting the gel and generating a fluid phase of tetramers whose arm ends are unable to bind to other tetramers being capped by monomers. The entire process, being based on the low-valence equilibrium gel concept, is fully reversible.

### 2.4. Thermodynamic stability of equilibrium gels

In principle, particle systems at low $T$ should be metastable with respect to some ordered phase and slowly nucleate a crystal. Interestingly enough, it has been shown that in limited valence systems, when bonds between particles are highly flexible, open crystals are strongly destabilized, so much that the liquid phase becomes the thermodynamically stable phase [74•]. This suggests that equilibrium gels of patchy particles can offer examples of thermodynamically stable equilibrium gels. The DNA nanostars are a typical example of colloidal particles which can form highly flexible bonds. Indeed, the four arms are highly mobile, due to the presence of unpaired bases in the star center. It is thus not surprising that numerical simulations based on the oxDNA model [75], for the specific case of DNA nanostar gels, have confirmed the thermodynamic stability of the gel with respect to the crystal [76]. Other observations of flexibility-induced stability of the disordered phase have been reported in Ref. [77].

### 2.5. Biological applications

Proteins also provide examples of patchy colloidal particles. Hydrophobic patches or charged amino acids [78] often conspire to generate highly non-directional interaction potentials. Proteins are often characterised by low critical volume fractions and by open crystals, indication of a significant directional component in the
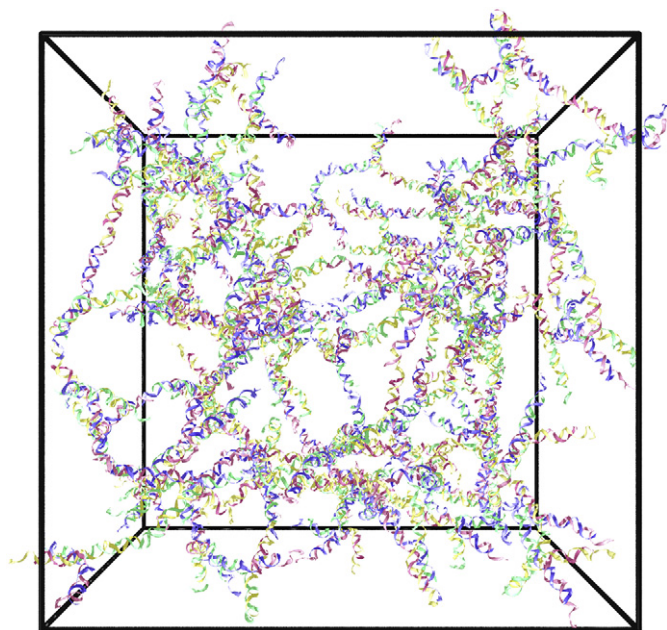


**Fig. 3.** Representation of an all-DNA gel formed by DNA tetramers, adapted from Ref. [62••]. Each nano star is formed by four DNA strands of 49 bases each. Binding between different nano-stars is provided by a self-complementary six-bases sequence located at the end of each arm.
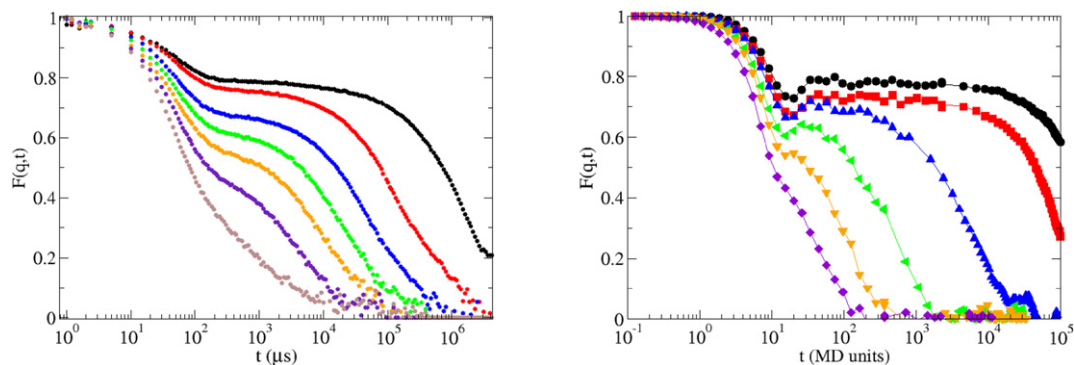
**Fig. 4.** Left: Density auto-correlation function $F(q,t)$ measured by Dynamic Light Scattering (DLS) for trivalent DNA nanostars at a concentration of 12 mg/ml, with 150 mM added NaCl and various temperatures. From top to bottom: $T = 40.1, 34.6, 32.2, 29.7, 27.5, 25.5, 18.1$ °C (from Ref. [64]); (right) The same correlation function calculated in Molecular Dynamics simulation of particles interacting via the $N_{max}$ [24•,65] model, with valence 3, at packing fraction $\phi = 0.20$ and scaled temperatures, from top to bottom, $T^* = 0.075, 0.08, 0.10, 0.125, 0.15, 0.17$. In both systems, both the plateau height and the relaxation time increase on cooling.

inter-protein interaction [79]. It is thus expected that the concept of equilibrium gel will be of relevance in biological applications. A preliminary indication in this direction can be found in the Ph.D. thesis of Jing Cai in the group of Alison M. Sweeney [80••]. In this beautiful work, the squids cellular lens is investigated to find out the biological origin of the lens peculiar density gradient. The results suggest that squids lens proteins form a gel with a gradient in the gel concentration, that correlates with a gradient in the valence of the expressed proteins.

The physics of limited valence has also been invoked to interpret the aggregation process in proteins induced by the presence of multivalent ions. Interestingly, patches are activated by the presence of the ions, allowing external control on the aggregation process. The experimental investigation of Human Serum Albumin in the presence of YCl$_3$ [57,81] has shown the presence of a metastable liquid-liquid phase transition, in which the coexisting liquid density progressively increases with the number of patches in the system, i.e. the salt concentration. Theoretical modeling of the system via patchy particles consistently explains the experimental results [82••]. Finally we note that patchy particle models can explain the experimental variation of the phase behavior for different mutants of the same protein [83••] or for the modifications induced by fluorescent labelling [84].

### 2.6. Other evidence

Recent works by Dudukovic and Zukoski have reported the evidence of the formation of equilibrium molecular gels in a solution of Fmoc-diphenylalanine (Fmoc-FF) (see Fig. 2) in dimethyl sulfoxide. Upon addition of water or change of pH, the molecules self-assemble into fibers, which then form a space-filling fibrous network with large stiffness even at very low volume fractions [56]. The molecules interact primarily via anisotropic reversible interactions, associated to strong π–π stacking bonds of the side chains and hydrogen bonds. The gel formation, occurring at sufficiently high $T$ in the absence of phase separation, has been interpreted in terms of reversible equilibrium gels [85•], in analogy with patchy particle systems. Finally, a series of works by Odriozola and coworkers [55,86,87•] investigated the role of the shape in attractive particles, by examining the phase behavior of attractive ellipsoids (see Fig. 2). Even if the particles interact with a simple square-well potential, the anisotropic shape restricts the formation of possible bonds, providing limited valence to the particles. Extensive Monte Carlo simulations have shown that the gas-liquid critical point moves towards low particle densities in full analogy with patchy spheres [86]. Furthermore, for oblate particles, also the critical temperature extrapolates to zero as in patchy spheres, while in prolate ones it seems to approach a finite value. The variation of

the critical point is accompanied by a shrinking of the phase coexistence region and consequently the existence of a liquid phase at very low particle densities. This opens up the possibility to observe equilibrium gels in this new class of systems. Recent calculations suggest that equilibrium gel formation should be facilitated for rod-like rather than disk-like attractive ellipsoids [87•].

## 3. Percolation at gelation

Some systems show gelation in equilibrium crossing (or close to) the percolation line. Despite these systems are not equilibrium gels of limited valence particles, they share with them several interesting features.

A very interesting gel-forming system of this type, first studied by Appell and co-workers [88••,89], is composed by microemulsion droplets in solution with telechelic polymers. In this system the polymer core prefers to be surrounded by the solvent, while the two ends preferentially explore the interior of the microemulsion. When the two ends are located in different droplets, they effectively provide a transient link between them. The fraction of telechelic polymers in solution thus controls the effective average valence. Interestingly, in this system gelation can coincide with percolation. Indeed the lifetime of the inter-droplets bond is controlled by the average residence time of the polymer end inside the microemulsion. As a result, the transient network gel restructures itself on the same time scale as the bond lifetime. By tuning the residence time (a quantity that is completely decoupled from the number of inter-droplets bonds) it is thus possible to control the location of the gelation line [90•]. For very long residence times, gelation coincides with percolation [90•]. Such a system provides an interesting example of decoupling the bond lifetime from the strength of the interparticle interaction [11,12]. The density autocorrelation functions measured by DLS show an increasing plateau on increasing the concentration of telechelic polymers [88••]), as in the DNA nanostars systems. But differently from the DNA nanostar case, the $\alpha$-relaxation time does not depend on the number of bonds, a clear evidence of the separation of the bond lifetime from the thermodynamics controlling the aggregation of the microemulsion droplets. Interestingly, the $\alpha$-relaxation time is wavevector independent [88••], similarly to the DNA nanostar case.

Another system in which dynamic arrest and gel formation appear to be related to the crossing of the percolation line is provided by octadecyl-coated silica particles suspended in n-tetradecane [91,92]. In this system the inter-particle potential is tuned by temperature. The $T$ affects the brush conformation leading to a liquid-to-solid phase transition of the brush itself. Static scattering experiments suggest that the inter-particle potential can be rather well approximated with a square-well potential of width 1% of the particle

diameter [91]. However, accurate event-driven simulations [93] have shown that for this theoretical model the bond lifetime along the percolation locus is too fast to generate gelation. The disagreement between numerical and experimental studies suggests that in this system the conformational transition of the brush may at the origin of the large bond lifetime at percolation.

## 4. Conclusions and future directions

We expect a significant activity focused on equilibrium gels in the next years. Several interesting problems need to be tackled. To start with, an effort is requested to move from the design of single particles to the production of bulk quantities of them. Indeed, while a vast zoo of novel patchy colloids and colloidal molecules has been reported in recent years, scalability in their synthesis and bulk production has been rarely achieved. Only production of large quantities of limited-valence particles, with designed and controlled connectivity, bond strength and bond lifetime, will make it possible — in addition to the few experimental systems studied so far — to test the predictions of theoretical and numerical investigations and to study in full details the self-assembly process and the collective response of equilibrium gels. At the same time, it will be possible to clarify the analogies and differences between equilibrium gels of limited valence particles and physical gels in which gelation is associated to crossing of some sort of a percolation line.

We also foresee a significant effort towards deepening the connection between patchy colloidal particles and proteins. More specifically, we need to quantify the protein-protein effective interaction and its patchiness. This will also require understanding cases in which isotropic interactions coexist with more directional ones [94], still retaining the windows of densities where equilibrium gel forms.

Concerning the dynamics of equilibrium gels of limited valence particles, several questions are still open:

1. Is there a peculiar dynamics associated to the crossing of the glass and equilibrium gel lines [28•,65]? Is the competition between arrest due to bonding and arrest due to excluded volume caging capable to produce anomalous dynamics as in the case of short-range attractive colloids[95]? Simulation studies seem to indicate that indeed extremely long relaxation times are observed in the cross-over region, associated to the emergence of logarithmic dynamics [65,96]. A confirming experimental investigation is still missing.

2. Bond flexibility has recently been shown to have a large impact on the relative thermodynamic stability of equilibrium gels compared to the one of crystals [74•]. Has flexibility a similar role also on the network restructuring dynamics and hence on its mechanical properties? Preliminary numerical results seem to suggest that the activation energy for bond breaking, controlling the Arrhenius low $T$ behavior of the dynamic properties depends significantly on the network flexibility. Colloidal particles with controlled flexibility have been recently fabricated [97], possibly providing a suitable model system for experimentally addressing this question.

3. A wave vector independent relaxation time $\tau_\alpha$ characterise the slow decay of the density fluctuations in DNA-gels [30] and microemulsion droplets linked by telechelic polymers [88••]. What is the microscopic mechanism controlling such length-scale invariant process? Does it have a counterpart in atomic and molecular network-forming liquids? How is the bond lifetime related to $\tau_\alpha$ and to the system viscosity? What are the microscopic mechanisms controlling density and stress fluctuations in these materials? Very recent experiments [98] seem to suggest that the peculiar length-scale invariant slow mode in DNA gels arises from fluctuations in the local bulk modulus induced by topological rearrangement. In this respect one could speculate that this mechanism is generic in network systems, both atomic and colloidal. The time scale of bond breaking and reforming should thus control all bulk dynamic quantities. Experimental studies and simulations tailored to explore the small wave vector region can provide an answer to these questions.

We are confident that these questions will be answered in the near future.

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## References•,••

[1] Geiger A, Stillinger F, Rahman A. J Chem Phys 1979;70:4185.
[2] Stanley HE, Teixeira J. J Chem Phys 1980;73:3404.
[3•] Sciortino F. Eur Phys J B 2008;64:505.
        This article calls attention on the analogies between colloidal gels and network forming liquids.
[4] Colby R, Rubinstein M. New-York: Oxford University.2003,274–81.
[5] Tanaka F. Polymer physics: applications to molecular association and thermoreversible gelation. Cambridge University Press.; 2011.
[6••] Zaccarelli E. J Phys Cond Mat 2007;19(32):323101.
        A very clear review of the different routes to colloidal gelation. Recommended as an introduction to gelation in particle systems.
[7] Sciortino F, Buldyrev SV, Michele CD, Foffi G, Ghofraniha N, Nave EL, Moreno A, Mossa S, Saika-Voivod I, Tartaglia P. et al. Comp Phys Comm 2005;169:166.
[8] Sciortino F, Zaccarelli E. Curr Opin Solid State Mater Sci 2011;15:246.
[9•] de Las Heras D, Tavares JM, Telo da Gama M. Soft Matter 2012;8:1785.
        An evolution of the equilibrium gel toward more complex physical conditions. Two interpenetrating networks.
[10] Lindquist BA, Jadrich RB, Milliron DJ, Truskett TM. J Chem Phys 2016;145:074906.
[11] Del Gado E., Fierro A, de Arcangelis L., Coniglio A. Phys Rev E 2004;69:051103.
[12] Saika-Voivod I, Zaccarelli E, Sciortino F, Buldyrev SV, Tartaglia P. Phys Rev E 2004;70:041401.
[13•] Verhaegh NA, Asnaghi D, Lekkerkerker HN, Giglio M, Cipelletti L. Physica A 1997;242:104.
        One of the first evidences that the formation of depletion gels is triggered by spinodal decomposition.
[14] Poon W, Selfe J, Robertson M, Ilett S, Pirie A, Pusey P. J Phys II 1993;3:1075.
[15] Lu PJ, Zaccarelli E, Ciulla F, Schofield AB, Sciortino F, Weitz DA. Nature 2008;453:499.
[16] Buzzaccaro S, Rusconi R, Piazza R. Phys Rev Lett 2007;99:098301.
[17] Leone M, Sciortino F, Migliore M, Fornili S, Vittorelli M. Biopolymers 1987;26:743.
[18] Chiappini M, Eiser E, Sciortino F. Eur Phys J E 2017;40:7.
[19•] Carpineti M, Giglio M. Phys Rev Lett 1992;68:3327.
        Important experimental work showing that DLCA gels structure shows the signatures of an underlying spinodal decomposition.
[20] Cipelletti L, Manley S, Ball R, Weitz D. Phys Rev Lett 2000;84:2275.
[21] Sciortino F, Tartaglia P. Phys Rev Lett 1995;74:282.
[22•] Campbell AI, Anderson VJ, van Duijneveldt JS, Bartlett P. Phys Rev Lett 2005;94:208301.
        Experimental evidence of filamentous colloidal gels based on competing interactions.
[23] Toledano JCF, Sciortino F, Zaccarelli E. Soft Matter 2009;5:2390.
[24•] Zaccarelli E, Buldyrev SV, Nave EL, Moreno AJ, Saika-Voivod, Sciortino F, Tartaglia P. Phys Rev Lett 2005;94:218301.
        The first numerical model showing the shrinking of the phase-coexistence region on reducing the valence.
[25••] Bianchi E, Largo J, Tartaglia P, Zaccarelli E, Sciortino F. Phys Rev Lett 2006;97:168301.
        This article introduces the empty liquid concepts exploiting the Wertheim theory applied to limited valence patchy particles.
[26] Bianchi E, Tartaglia P, La Nave E, Sciortino F. J Phys Chem B 2007;111:11765.

        • of special interest.
        •• of outstanding interest.

[27] Bianchi E, Tartaglia P, Zaccarelli E, Sciortino F. J Chem Phys 2008;128:144504.
[28•] Krzakala F, Tarzia M, Zdeborová L. Phys Rev Lett 2008;101(16):165702.
      This article presents a theoretical study based on a lattice model of the
      dynamics and thermodynamics in a limited valence system. Relevant is the
      investigation of the crossing of the ideal glass and gel lines.
[29] Sastry S, La Nave E, Sciortino F. J Stat Mech Theory Exp 2006;2006:P12010.
[30] Biffi S, Cerbino R, Nava G, Bomboi F, Sciortino F, Bellini T. Soft Matter
      2015;11:3132.
[31] Lekkerkerker H, Poon W-K, Pusey P, Stroobants A, Warren P. EPL (Europhys
      Lett) 1992;20:559.
[32] Anderson VJ, Lekkerkerker HN. Nature 2002;416:811.
[33] Lekkerkerker HN, Tuinier R. Colloids and the depletion interaction.833.
      Springer.; 2011.
[34] Koumakis N, Petekidis G. Soft Matter 2011;7:2456.
[35] Asakura S, Oosawa F. J Chem Phys 1954;22:1255.
[36] de las Heras D, Tavares JM, Telo da Gama M. J Chem Phys 2011;134:104904.
[37••] Glotzer SC, Solomon MJ. Nat Mat 2007;6:557.
      The first seminal review on patchy colloidal particles.
[38] van Blaaderen A. Science 2003;301:470.
[39] Perro A, Reculusa S, Ravaine S, Bourgeat-Lami E, Duguet E. J Mater Chem
      2005;15:3745.
[40] Jiang S, Chen Q, Tripathy M, Luijten E, Schweizer KS, Granick S. Adv Mater
      2010;22:1060.
[41] Jiang S, Granick S. Langmuir 2009;25:8915.
[42] Kraft DJ, Groenewold J, Kegel WK. Soft Matter 2009;5:3823.
[43] Chen Q, Bae SC, Granick S. Nature 2011;469:381.
[44] Chen Q, Diesel E, Whitmer JK, Bae SC, Luijten E, Granick S. J Am Chem Soc
      2011;133:7725.
[45] Kraft DJ, Ni R, Smallenburg F, Hermes M, Yoon K, Weitz DA, van Blaaderen A,
      Groenewold J, Dijkstra M, Kegel WK. Proc Natl Acad Sci 2012;109:10787.
[46] Wang Y, Wang Y, Breed DR, Manoharan VN, Feng L, Hollingsworth AD, Weck
      M, Pine DJ. Nature 2012;491:51.
[47] Pawar AB, Kretzschmar I. Macromol Rapid Comm 2010;31:150. http://dx.doi.
      org/10.1002/marc.200900614.
[48] Pawar AB, Kretzschmar I. Langmuir 2008;24:355.
[49] Kamalasanan K, Jhunjhunwala S, Wu J, Swanson A, Gao D, Little SR. Angew
      Chem Int Ed 2011;50:8706.
[50] Yi G-R, Pine DJ, Sacanna S. J Phys Condens Matter 2013;25:193101.
[51•] Sacanna S, Korpics M, Rodriguez K, Colón-Meléndez L, Kim S-H, Pine DJ, Yi GR.
      Nat Commun 2013;4:1688.
      A recent review on a method to generate a new zoo of anisotropic colloids.
[52] Duguet É, Hubert C, Chomette C, Perro A, Ravaine S. C R Chim 2016;19:173.
[53] Kern N, Frenkel D. J Chem Phys 2003;118:9882.
[54] Ruzicka B, Zaccarelli E. Soft Matter 2011;7:1268.
[55] Meneses-Juarez E, Varga S, Orea P, Odriozola G. Soft Matter 2013;9:5277.
[56] Dudukovic NA, Zukoski CF. Langmuir 2014;30:4493.
[57] Zhang F, Roth R, Wolf M, Roosen-Runge F, Skoda MW, Jacobs RM, Stuzucki M,
      Schreiber F. Soft Matter 2012;8:1313.
[58••] Ruzicka B, Zaccarelli E, Zulian L, Angelini R, Sztucki M, Moussaïd A, Narayanan
      T, Sciortino F. Nat Mat 2011;10:56.
      The first experimental observation of an equilibrium gel in laponite.
[59] Pujala R, Joshi N, Bohidar H. Colloid Polym Sci 2015;283:2883.
[60] Corezzi S, De Michele C, Zaccarelli E, Tartaglia P, Sciortino F. J Phys Chem B
      2009;113:1233.
[61] Corezzi S, Fioretto D, Sciortino F. Soft Matter 2012;8:11207.
[62••] Rovigatti L, Bomboi F, Sciortino F. J Chem Phys 2014;140:154903.
[63] Biffi S, Cerbino R, Bomboi F, Paraboschi EM, Asselta R, Sciortino F, Bellini T. Proc
      Nat Acad Sci 2013;110:15633.
      The first experimental observation of the effect of the valence on the colloid-
      rich and colloid-poor phase separation.
[64] Bomboi F, Biffi S, Cerbino R, Bellini T, Bordi F, Sciortino F. Eur Phys J E Soft Matter
      2015;38:1.
[65] Zaccarelli E, Saika-Voivod I, Buldyrev SV, Moreno AJ, Tartaglia P, Sciortino F. J
      Chem Phys 2006;124:124908.
[66] Rovigatti L, Capone B, Likos CN. Nanoscale 2016;8:3288.
[67] Rovigatti L, Kantorovich S, Ivanov AO, Tavares JM, Sciortino F. J Chem Phys
      2013;139:134901.

[68•] Tlusty T, Safran SA. Science 2000;290:1328.
      A seminal investigation of the importance of topological effects on the phase
      coexistence. Dipolar hard spheres are de facto interpreted as a temperature
      controlled valence system.
[69] Russo J, Tavares JM, Teixeira PIC, Telo da Gama MM, Sciortino F. Phys Rev Lett
      2011;106:085703.
[70] Russo J, Tavares JM, Teixeira PIC, Telo da Gama MM, Sciortino F. J Chem Phys
      2011;135:034501.
[71] Roldán-Vargas S, Smallenburg F, Kob W, Sciortino F. Sci Rep 2013;3:
[72] Roldán-Vargas S, Smallenburg F, Kob W, Sciortino F. J Chem Phys
      2013;139:244910.
[73] Bomboi F, Romano F, Leo M, Fernandez-Castanon J, Cerbino R, Bellini T, Bordi F,
      Filetici P, Sciortino F. Nat Commun 2016;7:
[74•] Smallenburg F, Sciortino F. Nat Phys 2013;9:554.
      This article provides evidence that flexible bonds between limited valence par-
      ticles can give rise to disordered systems which are thermodynamically stable
      respect to crystals at all temperatures.
[75] Ouldridge TE, Šulc P, Romano F, Doye JP, Louis AA. Nucleic Acids Res
      2013;41:8886.
[76] Rovigatti L, Smallenburg F, Romano F, Sciortino F. ACS nano 2014;8:3567.
[77] Whitelam S, Tamblyn I, Haxton TK, Wieland MB, Champness NR, Garrahan JP,
      Beton PH. Phys Rev X 2014;4:011044.
[78] Li W, Persson BA, Morin M, Behrens MA, Lund M, Zackrisson Oskolkova M. J
      Phys Chem B 2015;119:503.
[79] McManus JJ, Charbonneau P, Zaccarelli E, Asherie N. Curr Opin Colloid Interface
      Sci 2016;22:73.
[80••] Cai J, Townsend J.P., Dodson T.C., Heiney P.A., Sweeney A.M. Publicly Accessible
      Penn Dissertations.2015. under review (2017)
      Outstanding experimental study of the biological function of equilibrium gels.
[81] Zhang F, Roosen-Runge F, Sauter A, Wolf M, Jacobs RM, Schreiber F. Pure Appl
      Chem 2014;86:191.
[82••] Roosen-Runge F, Zhang F, Schreiber F, Roth R. Sci Rep 2014;4:7016.
      A combined experimental and theoretical study demonstrating that multiva-
      lent ions can control the effective valence in protein-protein interactions.
[83••] Fusco D, Headd JJ, De Simone A, Wang J, Charbonneau P. Soft matter
      2014;10:290.
      An important study of the possibility to interpret protein-protein interac-
      tions in terms of patchy interactions, where each patch is accurately modeled
      through a characterization of the crystal contacts.
[84] Quinn M, Gnan N, James S, Ninarello A, Sciortino F, Zaccarelli E, McManus J.
      Phys Chem Chem Phys 2015;17:31177.
[85•] Dudukovic NA, Zukoski CF. Soft matter 2014;10:7849.
      This article provides evidence of equilibrium gel formation in molecular gela-
      tors.
[86] Varga S, Meneses-Juarez E, Odriozola G. Soft Matter 2013;9:11178.
[87•] Varga S, Meneses-Júarez E, Odriozola G. J Chem Phys 2014;140:134905.
      This article shows that particle shape can influence the effective valence and
      give rise to empty liquid phases.
[88••] Michel E, Filali M, Aznar R, Porte G, Appell J. Langmuir 2000;16:8702.
      Seminal experimental work on a system showing gelation at percolation by
      decoupling the bond lifetime from the system thermodynamics. One of the
      first evidences of a wavevector independent relaxation process in transient
      networks.
[89] Filali M, Ouazzani MJ, Michel E, Aznar R, Porte G, Appell J. J Phys Chem B
      2001;105:10528.
[90•] Hurtado PI, Berthier L, Kob W. Phys Rev Lett 2007;98(135503):4.
      A theoretical description of a transient gel with decoupling of bond-lifetime
      and system thermodynamics.
[91] Eberle AP, Wagner NJ, Castañeda-Priego R. Phys Rev Lett 2011;106:105704.
[92] Eberle AP, Castañeda-Priego R, Kim JM, Wagner NJ. Langmuir 2012;28:1866.
[93] Foffi G, De Michele C, Sciortino F, Tartaglia P. Phys Rev Lett 2005;94:078301.
[94] Liu H, Kumar SK, Sciortino F. J Chem Phys 2007;127:084902.
[95] Sciortino F, Tartaglia P, Zaccarelli E. Phys Rev Lett 2003;91:268301.
[96] Chaudhuri P, Berthier L, Hurtado PI, Kob W. Phys Rev E 2010;81:040502.
[97] Chakraborty I, Meester V, van der Wel C, Kraft DJ. Nanoscale 2017;.
[98] Nava G, Rossi M, Biffi S, Sciortino F, Bellini T. Phys. Rev. Lett. 2017; (under
      review).