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Soft Condensed Matter Physics of Foods and Macronutrients

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TOC Blurb

This Review tackles how soft condensed matter physics can assist in the understanding of complex food systems, by relying on the foundations of established theories on polymers, colloids and surfactants to unravel the properties of food macrocomponents and the challenges associated with this task.

Key points

- The theoretical tools developed in soft condensed matter physics provide means to describe foods and macronutrients at several scales ranging from angstroms to tens of microns.
- Polymer physics can be employed to characterize the properties of polysaccharides and unfolded proteins, whose complex nature poses novel theoretical questions.
- Dispersions and gels based on proteins can be described by the physics of colloids and aggregates, and their phase diagrams can be rationalized accordingly.
- The structural properties of food emulsions and targeted delivery of macronutrients from lipid-based mesostructures can be studied and controlled with the aid of surfactants physics and transport theory.
- Some experimental soft-matter tools are to date underexploited in food science, which calls for further theoretical research in soft-condensed matter physics.

Abstract

Understanding food properties is paramount for enhancing features such as appearance, taste and texture, for improving health-related factors, such as minimizing the onset of allergies or improving the digestibility of nutrients, as well as for preserving food and extending its shelf-life. This Review discusses the challenges and opportunities offered by analysing foods as soft condensed matter systems. Emphasis is placed on the three main macronutrients constituting the main building blocks of foods: polysaccharides, proteins and lipids. Similarities and differences with synthetic polymers, colloids and surfactants are described. The Review also discusses the lessons that can be learned from soft matter approaches and the extent of their applicability to real foods.

[H1] Introduction

Natural and processed foods comprise a large component of many people's heritage and cultural background. From a materials perspective, foods challenge established theoretical and experimental approaches developed to study other families of soft materials. This can be ascribed to the exceptional complexity of food systems, which is ultimately due to the heterogeneous palette of physico-chemical properties displayed by their macromolecular constituents. Such complexity makes foods an ideal playground for interdisciplinary research, involving physicists, biochemists or material scientists. An appealing approach to study foods is provided by soft condensed matter physics, which gives unique perspectives for fundamental interpretation of their physical properties.

From a physical point of view, foods can be regarded as highly complex soft condensed matter systems in which the properties of the final product are determined by the interplay of features corresponding to several length, time and energy scales¹. For instance, it is common knowledge that cooking meat at high temperature results in a stiff steak. The reason for this increase in the elastic modulus involves the combined effect of the denaturation **[G]** of collagen proteins (at a scale of nanometers) and their consequent aggregation into networks (at a scale of micrometers and above)². More generally, the microscopic structure of foods and beverages plays a key role in their texture as perceived by the mouth³⁻⁵.

The food microuniverse encompasses the whole field of soft matter¹, including polymer physics, supramolecular aggregation and colloidal physics, and phenomena such as spontaneous phase separation, membrane elasticity and molecular transport, across length scales from angstroms to micrometres (Fig.1a). Improvements in experimental techniques in recent years have given unprecedented insights into these systems, enabling refinements of food processing techniques and the development of related biomaterials, thus providing a playground for benchmarking the applicability of classic theories as well as for developing new physical concepts.

This Review discusses the state of the art of our understanding of foods from the perspective of soft condensed matter physics. To this end, it relies on general concepts that are not specifically related to foods, but which when applied to food meet success, failure and new challenges. To tackle this task from the most general perspective, we focus on the main classes of macronutrients — carbohydrates, proteins and lipids — by drawing analogies (and pointing to differences) with model systems, namely polymers, colloids and surfactants (Fig.1b). On a general level, the observed features are obtained as a compromise between entropy and enthalpy, whose relative weights are set by comparison with the thermal energy $k_B T$, where T is the absolute temperature and k_B the Boltzmann constant. If the enthalpic terms are smaller than $k_B T$, the system is driven by fluctuations, smearing differences among states that have minimal differences in energy; in the opposite case, enthalpy and entropy both contribute to the free energy and provide the driving forces of the observed phenomena (Fig.1b).

We first discuss the role of water as a solvent, particularly its hydrogen-bond structure and dielectric properties. Then, we discuss the three main classes of macronutrients by considering their counterparts in soft condensed matter physics (Fig.1b). In particular, we analyze the single-molecule properties of polysaccharides with the lens provided by single-polymer physics; we discuss protein aggregation by considering colloidal systems; we interpret self-organization of lipids with the aid of the physics of surfactants. In all cases, we provide examples from the world of food systems and

critically review the extent to which theories can be applied, paving the way for an improved understanding of these challenging systems.

[H1] Water as a solvent

Virtually all processes involving foods take place in water-rich environments. Despite being the most common liquid on Earth, water is by far the most complex and debated one⁶. Its peculiar properties arise from hydrogen bonding, which induces short-range correlations⁷ and a dynamic network of transient links between molecules⁸. Moreover, when a solute also shows propensity to hydrogen-bond formation — which is the case for macronutrients — water solvation often leads to complex phenomena challenging the validity of established theories (see Box 1).

The thermodynamic anomalies of water can be understood as a consequence of a liquid–liquid phase transition at supercooled temperature⁹, whose existence is highly debated but increasingly supported by experimental evidence¹⁰. Although many studies of water are experimental or simulation-based, a recent analytical model including two-body contacts, local hydrogen bonds and twelve-body cooperative cages is able to capture most of the thermodynamic properties of water¹¹. Yet, many other aspects of water at extreme temperature, pressures and confinement remain to be fully explained¹².

Another important aspect of water is related to its role as a dielectric. At room temperature, water has a large dielectric constant ($\epsilon \simeq 80$), which has deep consequences for the electrostatic interactions involving macronutrients. A large ϵ ensures solubility of ions by imposing a low Bjerrum length. The Bjerrum length is defined as the distance at which the bare electrostatic interaction between two elementary charges ($e_0 = 1.6 \times 10^{-16}$ C) has a magnitude equal to the thermal energy $k_B T$

$$l_B = \frac{e_0^2}{4\pi \epsilon_0 \epsilon k_B T} \quad (1)$$

where $\epsilon_0 = 8.85 \cdot 10^{-12}$ F m⁻¹ is the absolute permittivity; in water at room temperature this gives $l_B \simeq 0.7$ nm. As discussed below, the low Bjerrum length makes ionic interactions in water particularly ‘short-sighted’ compared to vacuum and most other dielectrics. For example, any salt is more readily soluble in water than in alcohol or organic solvents.

Moreover, the mobile ions in solution preferentially locate around a charge of the opposite sign¹³. In this way, the overall repulsion between like charges is weakened, and decays exponentially with a scale given by the Debye length

$$l_D = \frac{1}{\sqrt{8\pi N_A l_B I}} \quad (2)$$

where I is the ionic strength of the solution in mM and N_A the Avogadro constant. To get a feeling for numbers, at room temperature water has $l_D \simeq 1$ nm for $I = 100$ mM, that is, a Debye length comparable to the size of a food macromolecule. The comparability of screening length and macromolecule size has ramifications for the properties of macronutrients, both at a single-molecule level and for the formation of aggregates, as discussed below.

[H1] Single-Polymer Physics of Macronutrients

Polymer physics is well-adapted to describe macromolecular food components. Some decades ago, the pioneering work of Pierre-Gilles de Gennes¹⁴ showed that many properties of polymer solutions depend exclusively on the string-like structure of macromolecules and on a few general features of their interaction with each other and with the surrounding solvent. Polymer physics remains the focus of active investigation, with new universal laws yet being uncovered only in recent years¹⁵⁻¹⁷.

[H2] Scaling laws

The basic description of a polymer depicts it as a chain of bonds connecting consecutive monomers. Entropy is maximized by a random orientation of bonds, but monomer–monomer and monomer–solvent interactions usually affect the final conformation of the polymer¹⁴. The interplay of these free-energetic contributions results in the overall size R of the chain scaling as a power-law of the polymer contour length L (Fig.2)

$$R = C_R L^\nu \quad (3)$$

where ν is a universal scaling exponent and the prefactor C_R depends on the microscopic features of the polymer. Importantly, this scaling relation is valid also for subchains, so long as they are large enough to overcome effects from the intrinsic stiffness of the polymer (see below), or, to borrow from fractal language, so long as the chain portion remains self-similar. R is usually described either by the end-to-end distance R_e of the polymer or by its radius of gyration R_g , which gives the average distance between a monomer and the centre of mass of the chain¹⁸.

The value of ν depends on the energy difference between monomer–monomer and monomer–solvent interactions. For a so-called θ -solvent, these interactions are equivalent, thus entropy dominates the free energy of the chain and R follows random-walk statistics (the freely-jointed chain model). In other words, $\nu = 1/2$ (Fig. 2a). Random-walk statistics have been reported for some food systems such as amyloid nanofibrils formed from the milk protein β -lactoglobulin¹⁹ (Fig.3a) and the naturally occurring polysaccharide κ -carrageenan in the presence of sodium stearyl lactylate²⁰, an additive used as thickener in processed foods. Nevertheless, it seems unlikely that these results stem from θ -solvent features, as this would require fine-tuned temperature and chemical conditions. As detailed below, a more refined mechanism may be at play, at least in the protein case.

For a poor solvent, monomer–monomer and solvent–solvent interactions are preferred, and the chain takes a compact conformation characterized by $\nu = 1/3$ (Fig. 2b). Moreover, at large polymer concentration, spontaneous aggregation may take place (see Box 1). Water is a poor solvent for globular proteins, as confirmed by the scaling $R_g \propto L^{0.34}$ reported for a database of thousands of proteins from the Protein Data Bank²¹. Analogously, internal subchains probed by Förster resonance energy transfer (FRET) show a scaling close to the expected value (Fig.3b). Nevertheless, the internal structure of a folded protein is not random, because the protein is adapted for the task to be performed in vivo; thus it is expected that such internal scaling does not always hold. A compact single-protein system showing self-similarity can be obtained by denaturing a protein and putting it back into native conditions, a procedure which can result in the formation of a homogeneous

globule²², in which the protein collapses onto a random compact conformation, and for which it is expected that internal scaling holds on a more general ground.

In a good solvent, monomer–solvent interactions are energetically favoured. Consequently, the polymer presents a swollen conformation characterized by monomer self-avoidance (a random coil). The extent of excluded-volume effects on chain conformation depends on the dimensionality d of the system. Flory theory yields the relationship $\nu = 3/(d + 2)$ (Fig. 2c) by considering the entropy of a freely-jointed chain and the overlap probability of a gas of monomers with the same concentration as the polymer system under inspection¹⁸. The results of Flory theory are in close agreement with values obtained from experiments and simulations in 2D and 3D, although in 3D a more precise estimation of the exponent gives $\nu \simeq 0.588$ (Ref. ²³), in agreement with renormalization-group predictions²⁴. Bio-polymers and food polymers are well described by the scaling laws predicted by polymer theory. For example, chemically-denatured proteins closely follow the expected exponent for $d = 3$ (Fig.3b), as shown using FRET²¹ and small-angle X-ray scattering (SAXS)²⁵. Similarly, at sufficiently large length scales, double-stranded DNA has $\nu \simeq 0.59$ (Fig. 3c), as measured via strong-adsorption atomic-force microscopy (AFM)²⁶. Analogous results have been reported for extracts of gluten proteins²⁷ and polysaccharides, such as sugars extracted from lactic acid bacteria²⁸ and κ -carrageenan in the presence of NaCl (Ref.²⁰). In 2D, the scaling behaviour of food systems such as lysozyme-based²⁹ and albumine-based³⁰ protein nanofibrils has been explored using AFM; at large length scales the exponent matches theory (Fig.3c).

A puzzling issue becomes evident when considering the scaling of amyloid fibrils **[G]**. In 3D, β -lactoglobulin fibrils follow random-walk statistics (Ref.¹⁹) (Fig.3a). However, in 2D, lysozyme systems and ovalbumine systems exhibit excluded-volume scaling^{29,30}. Random walk statistics do not change with dimensionality, and these systems are very similar to each other and in the same solvent conditions. Therefore, how is it possible that excluded-volume effects are relevant only in 2D? A possible answer relies on the way excluded volume interactions decrease with the dimensionality of the system. Excluded-volume effects are relevant only when their overall strength is larger than $k_B T$ (Ref.¹⁸). Therefore, these effects require a minimum length L^* of the polymer, to ensure enough monomer–monomer contacts. Because random encounters between monomers are more likely in 2D than 3D, a smaller threshold length is expected: $L^*_{2D} < L^*_{3D}$. Thus, it is possible that the contour lengths of amyloid fibrils lie between these two threshold values. However, dedicated work is needed to conclusively solve this issue, for instance by considering the concept of a thermal blob **[G]**, which provides an estimate of L^* based on Flory arguments¹⁸. In the present context, this problem epitomizes the challenges posed by food systems to well-established soft-matter theories.

[H2] Polymer rigidity

The scaling picture is further enriched when looking at short subchains, for which $\nu = 1$ (Fig.3c). The reason behind this behaviour is that the length scales considered are below the persistence length l_p of the polymer, which is related to its bending rigidity. l_p is defined as the characteristic length of the exponential decay of the bond–bond correlation function (Fig. 2d), and indicates how long a chain is needed to observe thermally-induced bending (Fig. 2e). At length scales shorter than l_p , the polymer is practically a stiff rod, which imposes $R \propto L$, that is, $\nu = 1$. l_p depends on the Young's modulus of the constituent material, the cross-section of the chain and temperature. Typical values encompass many orders of magnitude, from a few angstroms for proteins³¹ to millimeters for microtubules³².

For amyloid fibrils based on the food proteins β -lactoglobulin, lysozyme and serum albumine, l_p has been reported to be 1–4 μm , depending on the number of protofilaments composing the fibrils^{29,30,33}. Bundles of β -lactoglobulin fibrils cross-linked by pectin nanoparticles also have similar persistence lengths³⁴. However, different cross-linking mechanisms are expected to yield heterogeneous values of l_p , owing to the corresponding effective cross section of the bundle, so these results are not generally applicable to all fibril bundles. It is worth highlighting how processing conditions in food may lead to changes in l_p by four orders of magnitude, from native proteins³¹ to their fibrillar form once denatured and hydrolyzed [**G**]^{29,30,33}.

In contrast, the variation in persistence length of polysaccharides depends primarily on the particular macromolecule considered. For instance, l_p values of 5–10 nm have been reported for polysaccharides from lactic-acid bacteria²⁸. In the case of xanthan, different strains of the producing bacteria yield $l_p = 30\text{--}80$ nm, owing to differences in chemical details and the presence of secondary structure³⁵. A similar range of variability has been reported for amylose in various solvents^{36–39}, where monomer–solvent hydrogen bonding can induce a two-fold increase in rigidity³⁷. Finally, values of 10–60 nm have been reported for carrageenans, depending on chemical details, secondary structure and salt conditions^{40,41}. On a general level, the fundamental mechanisms linking the details of a polysaccharide to its persistence length depend on the chemical structure of the backbone, possible secondary structures, salt conditions and specific interactions, so that general trends on polymer rigidity remain highly system-specific.

[H2] Polyelectrolytes

The physics of charged polymers is of particular relevance for food systems, especially for polysaccharides, which in most cases host charged groups along the chain. Theoretical and experimental research on polyelectrolytes is one of the most active areas of research in polymer physics⁴². This activity is also due to the lack of a unified theoretical framework capable of describing the whole phenomenology, in contrast with other well-developed branches of polymer science. Although the scaling laws considered above still hold for charged polymers, the interaction between charges induces substantial modifications to chain flexibility.

Due to the presence of counterions, the interaction between two charges separated by a distance r is screened according to the Debye–Hückel potential¹³

$$U_{\text{el}} = k_B T \left(\frac{l_B}{r} \right) e^{-\frac{r}{l_D}} \quad (4)$$

where l_B is defined in equation 1 and l_D is defined in equation 2. The electrostatic repulsion between charges along the chain increases the stiffness of the polymer, which is usually accounted for by treating the persistence length as $l_p = l_p^0 + l_p^{\text{el}}$, where l_p^0 is the contribution from the intrinsic stiffness and l_p^{el} is the contribution from electrostatic interactions. The dependence of l_p^{el} on the ionic strength of the solution has been the focus of some debate. The classic theory of Theo Odijk⁴³, and Jeffrey Skolnick and Marshall Fixman⁴⁴ (OSF theory) treats the polymer conformation as a perturbation from a straight rod. From there, the cost in electrostatic energy induced by bending can be computed; the electrostatic contribution to the persistence length was shown to behave as $l_p^{\text{el}} \propto l_D^2 \propto 1/I$. Nevertheless, this dependence on ionic strength reproduces only the experimental data for stiff polymers⁴⁵, such as double-stranded RNA⁴⁶, and some doubt has been casted on the

applicability of OSF theory for double-stranded DNA^{47,48}. For flexible polymers, a variational approach predicts a weaker relation⁴⁵: $l_p^{el} \propto l_D \propto 1/\sqrt{I}$, which has been observed in flexible polymers, such as single-stranded DNA⁴⁹. Despite their experimental validation in a number of systems, both these theories have been challenged by simulations, for which a bead-spring model polymer gives a sublinear dependence $l_p^{el} \propto l_D^y$ ($y < 1$) (Ref.⁵⁰).

Experiments on food systems have also challenged the theoretical results. For instance, systematic force-spectroscopy experiments on the carbohydrate polymer hyaluronic acid at different ionic strengths reveal an intermediate scaling law $l_p^{el} \propto I^{-0.65}$ (Ref.¹⁶). The data from these experiments collapse onto a master curve upon a suitable rescaling of force and extension, indicating an underlying universal law. Although the physical origin of this universality is still an open question, simulations based on the Debye–Hückel potential reproduced the collapse of data, supporting the existence of a general law of polymer physics¹⁵. The behaviour of carrageenans is even more puzzling⁴⁰. At low and intermediate ionic strengths, l_p^{el} shows a sublinear dependence on l_D , in line with the simulation results of Ref.⁵⁰ but in contrast with theoretical predictions. Furthermore, for a group of observed molecules the persistence length shows a non-monotonic dependence on ionic strengths, and after a turning point it becomes an increasing function of I (Fig.3d). Current theories are unable to explain this non-monotonic behaviour and it is to be hoped that experimental work will spark interest among theoretical and numerical soft condensed matter scientists.

Another interesting feature of polyelectrolytes is provided by counterion condensation, first predicted by Gerald Manning⁵¹. Due to the approximate cylindrical symmetry of a polymer, when the linear charge density exceeds a critical value the gain in electrostatic energy from counterion localization near the chain overcomes the loss in translational entropy. For monovalent ions, the result is a massive condensation phenomenon⁵². Manning condensation occurs when the distance between consecutive charges is less than the Bjerrum length and the number of counterions involved is such that the final effective linear charge density corresponds to an average spacing of l_B between unit charges. Manning condensation affects the properties of the polymer. For instance, molecular dynamics simulations have shown the key role played by this mechanism in determining the electrophoretic mobility of homogalacturonans⁵³. Moreover, accounting for counterion condensation leads⁵⁴ to a prediction for the electrostatic contribution to the persistence length $l_p^{el} \propto I^{-0.7}$. This exponent is in line with the experimental results on hyaluronic acid¹⁶. Nevertheless, simulations based on Debye–Hückel theory¹⁵ (which by construction cannot show Manning condensation) also reproduce the correct exponent, thus other mechanisms are expected to be behind this result. In the case of carrageenans, Manning condensation could not account⁴⁰ for the observed behavior of l_p^{el} at any level. Quantitatively, the theoretical exponent is too large. Qualitatively, the non-monotonicity remains a mystery. Furthermore, it was also observed that carrageenans with linear charge density both below and above the critical threshold show similar behaviour, thus calling into question the relevance of Manning condensation for the determination of the properties of food systems, and suggesting a role for ion-specific interactions⁴⁰, a feature which is not accounted in classical polyelectrolyte theories.

[H2] Force spectroscopy

The response of a single polymer to an external pulling force provides invaluable information on the elastic properties of the chain. These properties can be extracted by fitting the smooth segments of

the force-vs-extension curve (FEC) with appropriate formulae from polymer physics^{18,55} (Fig. 3e), enabling an alternative route to evaluate the persistence length of the chain. Moreover, the presence of complex structures within a polymer chain can be identified via rupture events, where the FEC shows a sudden extension corresponding to force relaxation. Force spectroscopy has proven to be a versatile and reliable method to assess the single-molecule properties of biomolecules from its early days⁵⁶⁻⁵⁸ and is today a key tool in biophysics⁵⁹⁻⁶¹, providing an unprecedented level of detail on molecular processes and related free energies⁶², as well as an ideal testing ground for new theories⁶³. In the case of polysaccharides, force spectroscopy has nevertheless not yet been exploited to its full potential^{61,64}, in spite of an encouraging start, in which a pioneering work investigated the elastic response of the polysaccharide dextran using AFM pulling⁵⁸. There are however some notable exceptions to this trend^{16,34,65-67}. For instance, a recent investigation focused on the response of amylose to an external pulling force⁶⁵. The observed FECs (Fig.3e) could be rationalized by considering a freely-jointed chain in which each monomer could switch between two states corresponding to different atomic arrangements of the sugar ring, known as chair and boat configurations. The role of water on the conformational properties of amylose was assessed by performing several pulling experiments in the presence of water and propanol in different proportions, which enabled computation of the difference in free energy between the two states as a function of water content. Our hope is that this work will inspire further investigations of polysaccharides based on force spectroscopy, which is envisaged to give access to molecular details and have a major impact on food biotechnology.

[H2] Secondary Structure

The development of single-molecule techniques has fostered research probing the structural features of food macromolecules by direct visualization, for instance by transmission electron microscopy or AFM. AFM imaging in particular has proved to be a powerful tool, enabling the verification of proposed structural models by measuring the height profile along a molecule deposited on a substrate. For instance, amyloid fibrils based on β -lactoglobulin and lysozyme have been shown to arrange as purely-twisting or purely-bending ribbons, according to their width^{33,68}. These two geometrical arrangements can be distinguished using their height-profile fingerprints (Fig.3f). In the case of twisting ribbons, the twisting periodicity is related to the width of the ribbon via a universal law⁶⁹, which captures also the behavior of some fibrils unrelated to food systems⁷⁰.

Examples involving polysaccharides comprise investigations on the heterogeneous conformation of xanthan, including single-stranded coils and double-stranded branched structures or helices^{35,71}. Analogous studies have evidenced the existence of helical structures in xyloglucan⁷² and triple-stranded bundles in curdlan⁷³. In the case of carrageenans, the coil-helix transition was studied⁴¹, together with its dependence on the salt added to the solution⁴⁰ and the formation of aggregates of higher order⁷⁴. The observation of ion-specific features among monovalent salts (KCl, NaCl) contrasts with standard soft-matter physics models, which predict (via the Poisson–Boltzmann equation¹³) the behaviour of the system to depend only on the valency of the counterions. This example provides a further case of food systems being more complex than standard soft-matter theories.

[H1] Globular Proteins, Colloids, Aggregates

When considering larger length scales and polymer concentrations than those discussed above, the role of inter-molecular interactions in determining the physical properties of food systems is as important as — if not more important than — that of individual polymer properties.

For instance, it is well known that globular proteins in solution tend to attract each other, leading to spontaneous phase separation⁷⁵. The experimental phase diagrams derived for a number of protein systems show liquid, gel or crystal phases, resembling those obtained for colloidal solutions⁷⁶, which are more easily tackled both theoretically and experimentally. The physics of colloids is thus apt at qualitatively — and sometimes quantitatively — describing the mechanisms underlying the behaviour of protein systems.

[H2] Isotropic potentials

The simplest approach treats proteins as spheres of radius R interacting via an isotropic potential $U(r)$, that is, a potential depending only on the mutual distance r . In this regard, the classic Derjaguin–Landau–Verwey–Overbeek (DLVO) theory is the standard theoretical framework^{13,75} (Fig.4a):

$$U(d) = \frac{8\pi^2\sigma^2 R l_D^2 l_B}{e_0^2} k_B T e^{-\frac{d}{l_D}} - \frac{A R}{12d} \quad (5)$$

where $d = r - 2R$ is the minimum distance separating the surfaces of the colloids, σ is the surface charge density, e_0 the elementary charge and A the Hamaker constant **[G]** of the colloid. The first term on the right-hand side of equation 5 gives the electrostatic repulsion between two like-charged spheres in the Debye–Hückel approximation (compare with equation 4, which holds for point-like particles); the second term is the van der Waals attraction. $U(r)$ has an infinite well at $d \rightarrow 0$, which captures the tendency of colloids to aggregate (Fig.4a). To reach this stable aggregated state, the colloids must overcome a barrier whose height increases with R and decreases with I . In the case of proteins (R on the scale of nanometres), this height is of the order of $k_B T$ (Fig. 4a), implying that thermal fluctuations alone can trigger aggregation⁷⁵. The DLVO theory is customarily employed to rationalize experimental data, such as measurements of the second virial coefficient **[G]** of lysozyme solutions from light-scattering data^{77,78}. Nevertheless, it is by no means the only choice. Other popular models include the Baxter model⁷⁹, characterized by a short-range attraction in contrast to DLVO⁷⁵; depletion interactions^{80,81}, where attraction is induced by the presence of co-solvents, which maximize their translational entropy when the colloids are in proximity of each other; or simple-square well potentials, which are often preferred for practical convenience⁸²⁻⁸⁵.

All such potentials introduce severe approximations, and it is not clear to what extent they can be applied to protein systems. In this regard, a more general theoretical framework is provided by the extended law of corresponding states⁸⁶. According to the extended law of corresponding states, for any isotropic potential, the thermodynamic properties of the solution are universal once the variables are rescaled by three characteristic scales: attraction energy, hard-core repulsion length and potential range as quantified by the second-virial coefficient. Consequently, the existence of a master curve for binodals and spinodals (see Box 1 for their definition) has been shown for simulation data for several colloidal potentials^{77,78,87}. Experimental data also fall onto a master curve but can be reconciled with simulation results based on isotropic potentials only if temperature-dependent attraction wells are considered^{77,84}.

[H2] Proteins as Patchy Colloids

An important feature overlooked by the abovementioned isotropic potentials is the heterogeneity of protein surfaces, which contain patches with different charges or hydrophilicity (Fig.4b). This results in anisotropic protein–protein interactions, as evidenced by the specific molecular orientations observed in protein crystals⁷⁶. A more refined approach that tackles this issue is the theory of patchy colloids, in which proteins are modelled as spheres with sticky patches on their surface⁸⁸ (Fig.4b). The features of the phase diagram are primarily affected by the number of patches per colloid and integral properties such as the second virial coefficient, but are rather insensitive to the details of the potential⁷⁵. The theory of patchy colloids has been successfully employed to quantitatively reproduce the phase diagram of protein systems such as lysozyme and γ -crystallin^{89,90}, thus providing a key advance over isotropic potentials (Fig. 4c). Moreover, it was shown that the extended law of corresponding states can be extended to patchy systems⁹¹, thus explaining its success in describing protein systems despite the simplistic original approximation of isotropic potentials.

Patchy colloids are now widely employed to interpret experimental findings⁹²⁻⁹⁸. In parallel, they remain an active field of theoretical research⁹⁹, with focus on questions such as the interplay of anisotropy and electrostatics^{100,101} or effective interactions induced by patchy cosolvents¹⁰². In addition, dynamic phenomena are being investigated, such as the impact of anisotropic interactions on association kinetics **[G]**¹⁰³ and on the diffusive properties of the system^{94,104}.

[H2] Protein Aggregates

Under the right conditions, the presence of attractive interactions can lead to the formation of protein aggregates. Many aggregation pathways have been identified, and the final features of the clusters depend strongly on the particular protocol considered, such as increase in concentration, thermal denaturation or acidic stress. This section will focus on a few illustrative cases; a more thorough discussion can be found in reviews dedicated to the topic^{75,105-107}.

The interplay of short-range attraction and long-range repulsion, which are the main ingredients of the potentials considered in the previous sections, was theoretically predicted to lead to the formation of clusters of colloids¹⁰⁸ and experimentally reported for native lysozyme¹⁰⁹, bovine serum albumin¹¹⁰ and ovalbumin¹¹¹. In particular, SAXS measurements showed two peaks in lysozyme systems, which were ascribed to cluster-cluster (low- q , q the scattering vector) and intra-cluster (high- q) interactions¹⁰⁹. The position of the low- q peak was independent of protein concentration, suggesting a constant number of clusters of increasing size, in agreement with theory¹⁰⁸. Nevertheless, the interpretation of data was controversial enough to lead to a yet-unresolved¹⁰⁶ debate where the very existence of clusters was even questioned¹¹²⁻¹¹⁴, although more recent works seem to reinforce their presence^{115,116}. In the same system, the concentration dependence of short-time diffusion and viscosity has been assessed¹¹⁷, showing that quantitative agreement between theory and experiments is lost at high lysozyme concentration, thus calling for further theoretical research. Small-angle neutron scattering (SANS) has been used to study how attractive and repulsive interactions depend on ionic strength, protein concentration and temperature¹¹⁸. A sudden change in SANS profiles occurs beyond a critical temperature, at which thermal denaturation occurs and a different aggregation pathway of proteins becomes dominant, as discussed below.

Patchy-colloid physics has successfully explained the behaviour of several proteinaceous aggregates. For instance, it formed the basis for simulations that captured the experimentally observed features of gels of S-crystallin proteins in the squid eye lens, as well as albumin in pidan egg and monoclonal antibodies^{95,96,119}. Analogously, the experimental phase diagram of human serum albumin in the presence of the salt YCl_3 was nicely reproduced by a patchy particle model⁹⁸. At a given protein concentration c_p , experiments reveal a re-entrant phase transition when varying the salt concentration c_s , bound by the threshold values c^*, c^{**} (Fig. 4d). Outside this range, a homogeneous solution is found; for $c^* < c_s < c^{**}$, condensation is observed. Within this region a closed-loop inner region is further observed, where metastable liquid-liquid phase separation takes place. This complex phase diagram was nicely captured by a patchy model, where the trivalent ion Y^{3+} could transiently bind on specific spots on a protein and provide a sticky interaction with other proteins via salt bridges (Fig. 4d).

Protein aggregation following thermal denaturation is especially relevant for food systems, as it is directly related to gelation processes in cooking eggs¹²⁰ and meat^{2,121}, for example. Similarly, aggregation induced by mild acidification is relevant for systems such as yoghurt¹²². As the globular structure is lost, proteins expose hydrophobic patches which promote the formation of contacts between the denatured proteins. The fractal gel model⁷⁵ considers the aggregate as a self-similar object characterized by a size $\xi \propto M^{1/d_f}$, where M is the mass and $1 \leq d_f \leq 3$ the dimensionality of the cluster. $d_f = 1$ corresponds to filamentous aggregates, such as amyloid fibrils, and is typically obtained by hydrolyzing the protein under extreme conditions of temperature and pH¹⁹. Below the percolation threshold, aggregates corresponding to simple denaturation usually yield $d_f \geq 1.7$ (Ref.⁷⁵). For instance, β -lactoglobulin systems at low ionic strength exhibit $d_f = 1.7$ (Ref.¹²³), whereas stronger salt screening yields a more compact structure ($d_f = 2$)¹²⁴. Ovalbumin behaves in a similar manner upon varying pH¹²⁵: more compact gels are observed closer to the isoelectric point **[G]**, that is, for lower electrostatic repulsion. Soy globulin has $d_f = 1.8$ (Ref.¹²⁶) (Fig. 4e). Gluten proteins exhibit $d_f = 2$ both for proteins dissolved in water/ethanol mixtures and for deuterated water^{27,127,128}. Aggregation of complexes of polysaccharides and proteins has been recently analyzed¹²⁹, yielding a fractal dimension in line with the results reported for proteins ($d_f = 1.9$).

The fractal gel model also predicts the rheological properties of the gels obtained by aggregation. A scaling argument based on entropic considerations predicts the storage modulus **[G]**¹³⁰ $G \sim k_B T / \xi^3$, which assumes that the gel percolates the system with ξ as the mesh size, that is, the smallest scale at which the self-similarity can be present. Because self-consistency on local and global concentration C imposes $\xi \propto C^{1/(d_f-3)}$, this leads to the scaling $G \propto C^{3/(3-d_f)}$. Another model is based on enthalpic contributions from the connecting chains which, when present, are predicted to give a stronger exponent, namely $G \propto C^{(3+d_b)/(3-d_f)}$, where d_b is the fractal dimension of the connecting chain¹³¹. Employing the value measured from light scattering ($d_f = 2$, see above), analysis of the storage modulus for β -lactoglobulin gels gives¹²⁴ $d_b = 1.5$. Similarly, gels based on basil seed gum yield¹³² $d_f = 2.3$ and $d_b = 1.2$.

The main limitation of the fractal gel model is in its limited account of the polymer physics of the connecting chains. More refined models exist in the literature, but have not found wide application in studies on food-related systems. For instance, the affine thermal model includes the effects of cross-link length of the network (l_c) and persistence length of the constituting polymers¹³³:

$$G \sim k_B T \frac{l_p^2}{\xi^2 l_c^2} \quad (6)$$

Recently, this model was combined with the DLVO potential to assess the dependence of G on ionic strength I for networks of amyloid fibrils based on β -lactoglobulin and lysozyme¹³⁴. The predicted power laws were $G \propto I^{4.4}$ for β -lactoglobulin (Fig. 4f) and $G \propto I^{3.8}$ for lysozyme. These values closely match experimental results, thus showing the power of polymer-based predictions for food gels.

[H1] Physics of Lipids

The third pillar of the soft condensed matter physics of macronutrients is provided by surfactants, which are a good model for the behaviour of lipids in presence of water. Notable food examples are given by the microscopic structural evolution of edible emulsions rich in fat content under digestion, such as cow milk¹³⁵, human breast milk¹³⁶ and mayonnaise¹³⁷.

[H2] Flory-Huggins considerations

At a general level, surfactants are amphiphilic macromolecules, that is, the two ends interact differently with the solvent. As a result, the system tends to maximize the number of contacts between the solvent and the molecular end with more affinity and minimize the number of contacts at the end with less affinity. This tendency may easily result in microphase separation. Useful considerations come from applying the Flory–Huggins theory (Box 1) to lipids and to the model system provided by block copolymers **[G]**. In Flory–Huggins theory, spontaneous microphase separation takes place when $\chi N > 10$, where χ is the Flory–Huggins parameter and N the number of statistical segments in the polymer¹³⁸. For block copolymers $\chi \simeq 0.1$ (Ref.¹³⁹), thus a relatively large $N \simeq 100$ is needed for phase separation to occur. Assuming the same criterion for phase separation holds also in lipids, where large enthalpy leads to $\chi \simeq 3$, the condition $\chi N > 10$ implies that values as low as $N = 4$ are sufficient for witnessing phase separation, a condition easily fulfilled for most lipids¹. Therefore, self-aggregation of lipids is an enthalpy-driven process.

[H2] Geometrical structures of self-assembled lipids

Self-organized aggregates display a variety of structures, which differ in both topological and geometrical features (Fig.5). The most common aggregates are micelles, spherical droplets of lipids in which the lipid heads point either outward (direct mesophases) or inward (inverse mesophases). In the case of direct mesophases these droplets are dispersed in water where they can be arranged on a lattice with cubic symmetry ($Fd3m$). In the case of inverse mesophases, the water domains are confined within spheres. The spheres are organized in cubic-symmetric lattices ($Fd3m$ or fcc) with the lipid tails spanning the continuous domains, with or without the presence of additional organic solvents or oil to reduce the lipid tail frustration. Another familiar geometry is the lamellar structure, in which lipids form flat bilayers intercalated by water slabs. Two subgroups are identified according to whether the lipid tails are amorphous (L_α) or crystalline (L_c). A less trivial case is provided by direct hexagonal phases (Hex), in which the lipids form micellar-like cylindrical aggregates ordered in a honeycomb lattice in the transverse direction. Inverse hexagonal phases (H_{II}) are like Hex, but with reversed structural roles of lipids and water. Finally, the most intriguing geometries are provided by inverse bicontinuous cubic phases, in which a single lipid bilayer is arranged to form a minimal surface, characterized by zero mean curvature at each point, which encompasses the whole

mesophase. This creates two physically-separated yet identical sets of water channels with triple periodicity in space. The minimal surface followed by the lipid bilayer distinguishes between gyroid ($Ia3d$ space group), diamond ($Pn3m$) or primitive ($Im3m$) structures, whose defining lattices are characterized by coordination numbers equal to 3, 4 and 6, respectively (Fig.5).

H_{II} and cubic phases are possibly the most relevant geometries for foods, because they exist in excess water and are thus ideal hosts for delivery of drugs or nutraceuticals. Notably, these phases can either form macroscopic gel phases (bulk mesophases) or micro-sized dispersions (hexosomes and cubosomes). Apart from its topology, a mesophase is characterized by several geometrical features. The lattice parameter indicates the periodicity and usually lies in the range of ones to tens of nanometers; the radius of the corresponding nanochannels has values ranging from some angstroms up to a few nanometers. By systematic experiments, the phase diagrams of several lipids (some of the most important in the field of food technology being monoolein, monolinolein and phytantriol¹⁴⁰⁻¹⁴²) have been constructed, detailing the features of aggregates as a function of temperature and water content.

[H2] Theory of lipid mesophases

There have been several attempts to understand theoretically the observed phase diagrams. The simplest and most widespread theory considers the critical packing parameter $CPP = v/(a l)$, where v is the volume of the lipid tail, l is its length, and a is the area of the lipid head¹⁴³. When $CPP \approx 1$, the lipid has a roughly cylindrical shape and it is best accommodated in a lamellar geometry. For $CPP > 1$, the lipid tail occupies a larger volume than that accommodated by a cylindrical shape, thus inducing the formation of convex water domains. Consequently, inverse cubic phases and inverse hexagonal phases are favoured, with the latter preferred for larger CPP. Conversely, for $CPP < 1$ the volume spanned by the lipid tail is smaller than the corresponding cylinder, and direct phases are formed. The presence of hydrogen bonds with nearby water molecules induces a larger effective area of lipid heads¹⁴⁴. Therefore, because heating the system disrupts hydrogen bonds, an increase of CPP upon temperature increase is expected, which explains the observed transitions from L_α to cubic to H_{II} phases. Nevertheless, this theory cannot predict the changes occurring when hydration is increased.

Self-consistent field theories provide further insights on the matter. A first theoretical attempt captured the details of the conformations adopted by the lipid tails¹⁴⁵, but the agreement with experimental results was not satisfactory, probably due to the simplistic representation of lipid heads as rigid bodies¹³⁹. This issue was addressed in a subsequent model¹⁴⁴, in which lipid heads could reversibly form hydrogen bonds with co-located water molecules. Apart from correctly reproducing the thermotropic transition $L_\alpha \rightarrow \text{cubic} \rightarrow H_{II}$ upon heating, the theory also captured the transition from L_α to cubic obtained by increasing hydration. This provides a significant step forward in the understanding of mesophase physics. However, it cannot reproduce the whole experimental phase diagram, which remains a challenge. For example, the model in Ref.¹⁴⁴ predicts that the $Pn3m$ cubic symmetry is only metastable, thus failing to account for its dominant presence in the experimental phase diagram of monoglycerides at high hydrations.

Another problem that has generated some debate relates to the geometrical details of the lipid/water interface. In particular, two alternatives have been proposed based on the

incompatibility between constant mean curvature of the interface and constant thickness of the lipid bilayer. Assuming that the lipid/water interface has constant mean curvature provides a model that correctly captures the sequence of transitions that occur in the system upon increasing hydration¹⁴⁶. Nevertheless, the stretching stress this geometry introduces on the lipids has a high energetic cost, therefore a bilayer with constant thickness is instead expected to be favoured, corresponding to an interface parallel to the minimal surface¹⁴⁷. The competition between these two models has been partially solved by an experiment on phytantriol-based mesophases, in which reconstructed electron density maps agreed with expectations from the parallel-surface model, in contrast to the constant mean curvature theory¹⁴⁸ (Fig. 6a). However, it is unclear whether this result is specific to phytantriol or can be generalized to other lipids, and further work focusing on different systems is needed to find a conclusive solution to the problem.

[H2] Characterization and control

It is clear from the previous section that theories provide general guidelines, but cannot yet be used to design de novo a system with targeted features in lipid self-assembly. This shortfall has been compensated by a large set of studies aimed at understanding how topology and geometry of lipid mesophases are affected by a number of factors¹⁴⁹. Addition of co-surfactants usually results into swelling of both channels and lattice units, with a possible change of symmetry within the cubic family^{150,151}. If the co-surfactant is charged, swelling can further be induced via electrostatic interactions^{152,153} and controlled by adding salt¹⁵⁴ or tuning pH¹⁵⁵. Other strategies include pressure control¹⁵⁶ or direct changes in the structure of the composing lipids via enzymatic digestion^{157,158}.

Apart from indicating how to control the properties of mesophases, these studies are also pivotal for understanding the observations made for food systems. During digestion, the lipids in foods are subject to a change in pH from 1 in the stomach to 8 in the intestine, the action of enzymes, and the effects of bile salts¹³⁶. The separate impact of lipase¹⁵⁹ and bile salts¹⁶⁰ has been addressed on model systems. Moreover, the evolution of the structural features of lipid aggregates within foods during intestinal digestion has been followed using in vitro experiments mimicking the conditions in vivo. Detailed reports in the literature have been provided for mayonnaise¹³⁷, human¹³⁶ and bovine milk¹³⁵, as well as alterations induced by processing, such as homogenisation or freeze-drying, that is, sublimation from a frozen water phase¹⁶¹. In all cases, it has been shown that increasing pH and digestion time monotonically drives the system towards more complex structures characterized by higher internal surface. Indeed, the sequence of mesophases isotropic fluid \rightarrow $Fd3m$ \rightarrow H_{II} \rightarrow cubic is typically observed (Fig. 6b), in some cases together with a persistent lamellar phase¹³⁶. This invariant result has been suggested as a possible mechanism in vivo for transporting poorly soluble molecules through the aqueous environment of the gut¹³⁵.

[H2] Molecular transport across lipid mesophases

The interest in understanding the transport of molecules in mesophases stems from the need to characterize mechanisms likely to act in vivo¹³⁵ and the possibility of manufacturing edible systems for delivery of nutraceuticals¹⁶². Moreover, mesophases have also been proposed as nanoreactors for food reactions controlling aroma, taste or colour¹⁶³, whose yield is directly related to the diffusion properties of the reacting species. Importantly, incorporating micronutrients into lipid structures may impact the structure and function of the host mesophases¹⁶⁴.

Recent studies of molecular transport in lipid mesophases have addressed the impact of several features, such as the nature of diffusing molecules¹⁶⁵, the symmetry of the mesophase¹⁶⁴ and the hydration level¹⁶⁶. In particular, transport in bicontinuous cubic phases is significantly faster than in H_{II} . This has enabled the possibility of controlled triggering of the release behaviour of suitably-produced mesophases (Fig. 6c). For instance, a combination of phytantriol and vitamin E acetate provided a mesophase with $Pn3m$ symmetry at 30°C and H_{II} at 40°C¹⁶⁷. This enables control of the molecular release by temperature by inducing fast release by cooling the system below physiological temperature. Heating led to hampering of release. In another example, a pH-controlled switch has been obtained by combining monolinolein and linoleic acid, leading to slow diffusion at pH 2 and fast release at pH 7 (Ref.¹⁵⁵). Because these pH conditions are similar to those of stomach and intestine, the possibility has been opened of targeted molecular release in the intestinal tract (inset in Fig. 6c).

Differences in behaviour have also been reported among the various cubic symmetries. In particular, $Im3m$ exhibits faster transport compared to $Pn3m$. The two considered phases had different water content¹⁵¹, but the role of symmetry was elucidated by Brownian dynamics simulations¹⁶⁸. The simulations showed that if the water content is similar then it is expected that transport is faster in $Pn3m$ than in $Im3m$ (Fig. 6d), thus ascribing the experimental observation to the larger hydration of the considered $Im3m$ mesophase. Moreover, quantitative comparison between simulated and experimental diffusion coefficients highlighted the role of water mobility, which shows drastically different features when compared to the bulk phase. In particular, the presence of hydrogen bonds with the lipid heads induces slow water self-diffusion in the 3–4 layers in proximity of the lipid bilayer¹⁶⁹. Once the heterogeneity of water mobility observed in experiments was accounted for, simulation results showed quantitative agreement with the experimental data¹⁶⁸. However, further studies are needed before a complete understanding of molecular transport in lipid mesophases is achieved.

[H1] Perspectives

Despite the simplifications often introduced, the results from studies on polymers, colloids and surfactants provide tools to elucidate the properties of the primary constituents of foods, namely polysaccharides, proteins and lipids. However, in our Review, we have specifically tackled ‘well-behaving’ macronutrients and limited our discussion to situations where a single macronutrient interacts with water at thermodynamic equilibrium and with energies above the thermal fluctuation threshold ($E > k_B T$, see Fig.1b). In these cases, physical insight can be gained directly by equilibrium thermodynamics. However, most foods are often found far from equilibrium¹⁷⁰. For example, a colloidal dispersion of caseins, as found in skim milk, and a typical solution of a food polysaccharide such as xanthan, are both found individually at equilibrium, but when mixed they lead to a depletion-induced liquid-liquid phase separation which departs far from equilibrium binodal lines, following instead a nonequilibrium spinodal decomposition.

However, even in such a complex nonequilibrium evolving food system, some universal features are preserved. For instance, for the casein–xanthan mixture a universal signature has been reported for the structure factor which follows a master curve at any stage of the phase separation process —

from the initial to the intermediate and transition regimes — when plotted against the scattering vector (inverse of the characteristic length) times the characteristic length of the dominant structural feature¹⁷¹. Perhaps even more surprisingly, some other universal features are maintained even in the final stage of the arrested spinodal decomposition, in which a gel is formed. These features include the scaling of the shear modulus of the gel with the timescale of structural arrest¹⁷². This illustrates that some of the universal laws originally developed for model colloidal systems can assist in the understanding of complex food systems even beyond equilibrium thermodynamics.

As a further note, there are still some soft-matter tools that are underexploited in food contexts, such as force spectroscopy and polymer-based modelling of gel rheology, which could promote significant advances in food science in the coming years.

The understanding of food systems based on physical concepts has made it possible to devise new applications, which were unimaginable a decade ago. For example, protein self-assembly has been exploited in water purification¹⁷³, and in-vivo iron integration¹⁷⁴ ; lipid self-assembly has been suggested to improve bioavailability of vitamins in the blood stream¹⁷⁵. Complementary efforts from food scientists and soft condensed matter physicists are thus paramount to foster the development of new food technologies, which will provide unique opportunities to face the challenges of sustainable food production¹⁷⁶.

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Reviewer information

Box 1: Flory–Huggins theory and the challenges from hydrogen bonding

One of the cornerstones of soft condensed matter physics is provided by the Flory–Huggins theory of spontaneous phase separation of macromolecules¹⁸. Based on a mean-field approximation, the free energy F of a binary mixture of a polymer and a solvent is written as:

$$\frac{F}{k_B T} = \frac{\phi}{N} \ln \phi + (1 - \phi) \ln(1 - \phi) + \chi \phi(1 - \phi) \quad (7)$$

where ϕ is the volume fraction of the polymer, N the number of composing monomers (colloids or solvent molecules can be considered to have $N = 1$), and χ is the Flory interaction parameter, representing the nature and magnitude of monomer–solvent interactions. In a good solvent, χ is small or negative and only a mixed phase is present. In a poor solvent, $\chi > 0$ and spontaneous phase separation may occur: above the binodal line, a biphasic system is thermodynamically stable; between the binodal and spinodal lines the mixed phase is metastable, and phase separation occurs via nucleation and growth; above the spinodal line a rapid phase-separation process, known as spinodal decomposition, takes place without energy barrier (figure panel **a**). The temperature dependence of χ is usually well-described empirically by $\chi = A + B/T$. Usually, $B > 0$, that is, χ decreases for increasing temperature. In this case, the $\phi - T$ phase diagram is qualitatively the vertically-mirrored image of the $\phi - \chi$ diagram. Therefore, the $T(\phi)$ binodal is an upper critical solution line (UCSL), that is, phase separation occurs only below it. In some other cases, $B < 0$ and a lower critical solution line (LCSL) is instead found, that is, the $\phi - T$ phase diagram is qualitatively similar to the $\phi - \chi$ one.

Short neutral water-soluble polymers, such as polyethylene glycol and many neutral food polysaccharides, show closed-loop solution lines (CLSLs), that is, phase separation occurs only within a limited region (figure panel **b**). This finding is predicted by an extension of Flory–Huggins theory¹⁷⁷ (figure panel **c**), in which the presence of clusters accounts for the possibility of hydrogen bonding. In this model,

$$\frac{F}{k_B T} = \phi_0 \ln \phi_0 + \sum_{m=0}^f \frac{\phi_{m+1}}{N+m} \ln \phi_{m+1} + \chi \phi(1 - \phi) \quad (8)$$

where ϕ_0 is the volume fraction of unbound water, ϕ_1 that of unbound polymers, and ϕ_{m+1} that of m -clusters, that is, clusters consisting of a polymer plus m bound water molecules. f is the maximum number of bound water molecules that can be accommodated onto the polymer, and $\phi = \sum [N/(N+m)] \phi_{m+1}$ is the total volume fraction of the polymer clusters. Imposing chemical equilibrium among the clusters leads to $\phi_{m+1} = K_m \phi_1 \phi_0^m$, where K_m is a decreasing function of temperature. Assuming $B > 0$, temperature has two effects on the phase behaviour of the system. First, the Flory–Huggins parameter decreases with increasing temperature, leading to the appearance of UCSLs. Second, increasing temperature disrupts hydrogen bonds, making the solvent poorer and qualitatively acting like the case $B < 0$, promoting a phase diagram with LCSLs. For sufficiently short chains, these two effects compete, and a CLSL appears. For larger polymers, the biphasic region increases in size, and for long chains only the LCSL is present. This model precisely captures the experimental data (figure panel **b**), and shows the importance of polymer–water hydrogen bonding for features beyond the reach of the classic Flory–Huggins theory. This

framework has successfully rationalized the phase diagrams of various food systems, including methylcellulose¹⁷⁸ and hydroxypropyl cellulose¹⁷⁹.

Other expansions to the Flory–Huggins model have been proposed to describe the features of membraneless organelles in cells, particularly considering the presence of charges and heteropolymers^{106,180,181}. These examples show the limits of classical theories in describing real systems, and the importance of feedback from experiment to improve theoretical understanding.

a| Example phase diagram of a polymer–solvent system showing the binodal line (continuous red line), above which phase separation is thermodynamically stable, and spinodal line (dashed black line), which defines the region of metastability of the mixed phase. Φ : polymer volume fraction, χ : Flory interaction parameter. **b|** Experimental data for polyethylene glycol molecules of different molecular weights in water (points), together with theoretical prediction of extended Flory–Huggins theory (lines). **c|** Sketch of the clustering features captured by the extended Flory–Huggins theory. Panel **b** is reproduced from Ref. ¹⁷⁷.

Figure 1. Overview of the systems discussed in this Review. **a|** The systems organized by length scale. For each class of systems (written in black), a representative practical example is reported (red text and pictures). The length scales are separated into regions of single-molecule physics (small length scales) and supramolecular assemblies (large length scales), as indicated by the horizontal dashed line. **b|** The ‘magic triangle’ showing the analogies between food macronutrients and soft-matter model systems. The axis in the third dimension represents the typical energy of interactions within the system. If this energy is above the thermal energy, the physics of the system is free-energy-driven; if the energy is below the thermal energy the physics is driven by fluctuations. Panel **a** includes images reproduced from Ref.¹⁸² and Ref.⁹⁶.

Figure 2. Definitions of single-polymer physics. **a|** Typical conformation of a polymer in a θ solvent, for which the overall size R of the polymer (indicated by the circle) scales as its contour length L to the power of $1/2$. **b|** Typical conformation of a polymer in a poor solvent. The conformation is more compact than that in a θ solvent, and the scaling exponent is correspondingly reduced to $1/3$. **c|** Typical conformation of a polymer in a good solvent. Flory theory indicates that in this case the scaling exponent depends on the system dimensionality. In panels **a,b,c** all polymers have the same contour length. **d|** The bond correlation function $\langle \cos \phi(L) \rangle$ decays exponentially with characteristic length scale equal to the persistence length l_p . $\langle \dots \rangle$ denotes statistical average and $\phi(L)$ is the angle between two vectors tangent to the polymer and separated by L , as indicated in panel **e**.

Figure 3. Applications of single-polymer physics concepts to protein systems and polysaccharides. **a|** Scattering intensity profile I vs magnitude of scattering vector q for a solution of amyloid fibrils produced from β -lactoglobulin. The scaling exponent relating I and q for small q is the inverse of the single-molecule exponent $\nu=0.5$. **b|** FRET (Förster resonance energy transfer) measurements of radius of gyration R_g vs internal contour length L (rescaled by the bond length l_{bond}) for proteins at various denaturant concentrations. As the denaturant concentration increases, the system passes from poor solvent conditions (indicated by $\nu=0.34$) to good solvent conditions (indicated by $\nu=0.58$). **c|** Scaling regimes of the end-to-end distance R_e vs L below and above the persistence length, for ds-DNA in 3D (blue squares, data from Ref.²⁶) and lysozyme fibrils in 2D (red circles, data from Ref.²⁹). **d|** Persistence length vs concentration of NaCl for carrageenan chains in both coil and helical secondary structure conformations. Coil conformations show non-monotonic behaviour, which is not captured by current polyelectrolytes theories. The insets show typical configurations. **e|** Force vs extension curve for amylose at different hydration levels, together with the fit from a modified freely-jointed chain that includes the presence of boat and chair configurations. The upper curve corresponds to large hydration of the sample; the lower curve corresponds to low hydration. At sufficiently high hydration, a transition from chair configuration to boat configuration is observed upon pulling. **f|** Cartoons of amyloid fibrils with secondary structures arranged according to a helical ribbon (top, orange) and a twisted ribbon (bottom, cyan). The corresponding idealized height profiles, as would be measured by an AFM tip, provide a ‘fingerprint’ to recognize the structure under study. Panel **a** is reprinted from Ref.¹⁹. Panel **b** is adapted from Ref.²¹. Panel **d** is adapted from Ref.⁴⁰. Panel **e** is adapted from Ref.⁶⁵.

Figure 4. Physics of colloids and aggregates applied to food systems. **a|** Representative plot of the interaction energy U scaled by thermal energy $k_B T$ at room temperature, as a function of colloid separation d for a DLVO (Derjaguin–Landau–Verwey–Overbeek) potential (equation 5), for a protein system. The DLVO potential is a superposition of van der Waals attraction and electrostatic repulsion. The height of the aggregation barrier, which arises from electrostatic repulsion, becomes comparable to the thermal energy in globular proteins at room temperature. **b|** Patchy features of food proteins and example of a patchy colloid. In the case of proteins, the images show the charge distribution (red and blue indicate negatively-charged and positively-charged spots, respectively) obtained starting from the crystallographic structures (1BEB for β -lactoglobulin¹⁸³ and 1DPX for lysozyme¹⁸⁴) by means of the PBEQ solver¹⁸⁵. **c|** Phase diagram of protein systems and models. The temperature T and density ρ are rescaled by their values at the critical point (T_c and ρ_c respectively), identified as the maximum of the binodal. The binodal curve for γ -crystallin and lysozyme (full symbols) collapses onto the same master curve as patchy models (open squares and circles), whereas isotropic fluids behave differently (open triangles). **d|** Experimental phase diagram of solutions of human serum albumine in the presence of YCl_3 ; a patchy model with transient bonds reproduces the qualitative features of the phase diagram. c_p , protein concentration; c_s , salt concentration; c^* , c^{**} , threshold salt concentrations; C, crystal phase; L homogeneous-liquid phase; LLPS, liquid–liquid phase separation. **e|** Power-law dependence of the mass M_w of a soy-globulin aggregate on its hydrodynamic radius R_h indicates a self-similar structure, characterized by a fractal exponent $d_f \approx 1.8$. **f|** After rescaling by a suitable power of the concentration c , the storage modulus G_0 of gels based on β -lactoglobulin amyloid fibrils is a universal function of the ionic strength I of the solution, in close agreement with a theory combining the affine thermal model and DLVO. Different symbols correspond to different concentrations. Panel **c** is reproduced from Ref.⁸⁹. Panel **d** is adapted from Ref.⁹⁸. Panel **e** is adapted from Ref.¹²⁶. Panel **f** is reproduced from

Figure 5. Topological and geometrical features of some common inverse lipid mesophases. The top images sketch the microscopic geometry of the mesophase (lipid-containing regions are depicted in orange; water regions are in cyan); the bottom images highlight the underlying topology, showing the periodic lattice identifying each structure. Dashed links between lattice nodes indicate that the corresponding water channels are not connected. The right-hand panel is adapted from Ref.¹⁶⁸.

Figure 6. Physics of lipid mesophases. **a** | Electronic density map of a phytantriol-based mesophase with gyroid symmetry, supporting the validity of the parallel-surface model. **b** | Time evolution of mayonnaise microstructure under the action of lipase, as evidenced by profiles of SAXS (small-angle X-ray scattering) intensity vs magnitude of the scattering vector q . The inset images sketch the various structures displayed by the sample during the time of digestion. **c** | Controlled release achieved by tuning the topology and geometry of lipid mesophases via external stimuli. In this example the stimulus is switched off at time t_{off} and then switched back on at time t_{on} . Example stimuli include temperature¹⁶⁷ as an exogenous stimulus or pH¹⁵⁵ as an endogenous stimulus. A pH-based stimulus is relevant for targeted delivery in chosen tracts of the digestive system (inset). **d** | Brownian dynamics simulations results for effective diffusion of water within different cubic phases. The effective diffusion coefficient D normalized by the bulk value D_0 is plotted against water content within a channel (ϕ_{chan}). For low water contents, D is dictated by geometry for mesophases at similar hydration. Panel **a** is reprinted from ¹⁴⁸. Panel **b** is reproduced from ¹³⁷. Inset of panel **c** is reprinted from Ref.¹⁵⁵. Panel **d** is reprinted from ¹⁶⁸.

Glossary terms:

- **Denaturation:** loss of secondary, tertiary and/or quaternary structure of a protein due to temperature or chemical stress, for example
- **Amyloid fibrils:** protein and peptide-based fibrous aggregates with a characteristic cross-beta secondary structure.
- **Thermal blob:** the portion of chain length whose total interaction energy is of the order of $k_B T$
- **Hydrolyzed:** refers to when peptide chains are fragmented into shorter subunits due to chemical, enzymatic or thermal stimuli
- **Hamaker constant:** a quantity with the units of energy characterizing the van der Waals interactions between colloids
- **Second virial coefficient:** a quantity with units of volume describing the net two-body interactions between two particles; positive and negative values indicate net repulsion and attraction, respectively.
- **Association kinetics:** dynamic features of binding between particles, usually characterized by suitable rate constants.
- **Isoelectric point:** value of pH for which partial protonation induces a net zero charge in a molecule hosting several positively-charged and negatively-charged groups.
- **Storage modulus:** parameter with the units of pressure quantifying the elastic response of a viscoelastic material to an external stress
- **Block copolymers:** macromolecules obtained by covalently joining by one end two polymers with different physico-chemical properties.